WEST Search History

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DATE: Thursday, January 22, 2004

Hide?	Set Name	Query	Hit Count
		DB=USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR	
☐	L2	L1 and cross$	5
☐	L1	microsphere$ same (thermal$ adj2 condens$)	15

END OF SEARCH HISTORY

First Hit Fwd Refs

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L2: Entry 2 of 5 File: USPT Oct 21, 1997

DOCUMENT-IDENTIFIER: US 5679377 A
** See image for Certificate of Correction **
TITLE: Protein microspheres and methods of using them

Brief Summary Text (2):
Proteins have also been used to form microparticles or microspheres for drug delivery. R. C. Oppenheim, Polymeric Nanoparticles and Microspheres Guiot and Couvreur, editors, chapter 1, pp. 1-25 (CRC Press, 1986), reviews formation, properties and drug delivery using proteins. Most are crosslinked in solution using glutaraldehyde, or hardened at elevated temperatures. Unfortunately, there are problems with significant loss of biological activity of incorporated materials and lack of controlled size and in vivo degradation rates. For example, zein microspheres prepared as carriers for chemotherapeutic agents by crosslinking a zein solution containing the drug, as reported by Suzuki, et al., Chem. Pharm. Bull. 37(4), 1051-1054 (1989), were quite heterogeneous in size, and displayed incorporation of less than 30% of the drug. This same group reported in Chem. Pharm. Bull. 37, 757-759 (1989), that yield and size range were improved by addition of a catalytic amount of dl-camphorsulfonic acid and rapid addition of polyvinylpyrrolidone, a surfactant and binder. Incorporation of drug was still less than 35%, however. PCTUS87/02025 by Clinical Technologies Associates, Inc., reports the preparation and use for drug delivery of microspheres made of "protenoids", thermal condensation polymers of mixed amino acids. While these materials have useful properties, they are designed for specific applications and targeted release as a function of pH.

Brief Summary Text (3):
In a similar process, proteins have been used to make glutaraldehyde crosslinked beads incorporating bacteria for agricultural applications.

Brief Summary Text (5):
None of these methods of producing protein drug delivery devices can be used to incorporate high percentages of biologically active substances, especially labile substances, into uniform microspheres small enough to pass directly into the bloodstream when delivered orally, or with consistent release rates and sizes. None of the other processes yield a material having no binder or crosslinking agent present, that consists only of the natural protein. Moreover, while the above systems are useful for many applications, they are not appropriate for some applications, such as delivering orally administered drugs directly into the bloodstream. Oral administration of drugs is often the most desirable and convenient method. A need exists for systems that can successfully deliver these agents which have favorable release kinetics and allow the drug to be distributed or targeted in the host.

Detailed Description Text (2):
A method of delivery of a biologically active agent in which protein microspheres containing the agent are administered to a human or animal, or placed at a site for release of the agent by diffusion from and/or degradation of, the microspheres. The protein microspheres have several advantages. The protein matrix is a natural, biodegradable substance, which metabolizes in the body to peptides and/or amino acids. The proteins can be modified, chemically or enzymatically, to endow them

with desirable properties, such as a selected degradation rate. The process for making the microspheres from a protein solution does not require high temperature heating or cross-linking which could degrade material to be incorporated. Moreover, when used for drug delivery, the microspheres can be designed to be absorbed through the intestinal epithelium into the bloodstream and/or lymphatic system, or targeted to specific organs or phagocytic cells. The microspheres thereby have at least three distinct advantages for controlled delivery: protection of agents which would be attacked and/or degraded by the harsh conditions of the alimentary tract or enzymes in the blood; targeting of a site for release (such as phagocytic cells, mucosal membranes, or the blood, and controlled time and rate of release of agent.

Detailed Description Text (35):
The stability of the protein can be enhanced by crosslinking the protein prior to use in the phase separation process by the addition of an enzyme which catalyzes intr- and/or intermolecular crosslinking of the protein, such as transglutaminase, or protein disulfide isomerase. Transglutaminase and protein disulfide isomerase cause inter- and intramolecular crosslinking of the protein through the amino acids glutamine and cysteine, respectively. Transglutaminase catalyzes an acyl transfer reaction, in which the amide group of the amino acid glutamine is the acyl donor. Other enzymatic processes are known which alter the properties of proteins, before or after formation of the microspheres.

Detailed Description Text (39):
The charge on the protein can also be modified by crosslinking amino acids or polyamino acids to the protein, using glutaraldehyde or carbodiimide.

Detailed Description Text (40):
Proteins can be modified before or after formation of the microspheres. However, an advantage of the phase separation process is that harsh chemical or heat treatment of the protein after formation of the microspheres is not required. Accordingly, when modification of the protein using agents such as glutaraldehyde for crosslinking of the protein is desirable, the protein is treated prior to incorporation of the compound to be delivered and formation of the microspheres.

Detailed Description Text (75):
The charge or lipophilicity of the microsphere is used to change the properties of the protein carrier. For example, the lipophilicity of prolamine microspheres can be modified by covalently linking fatty acids to the proteins, and the charge modified by covalently linking amino acids or polyamino acids to the proteins, by deamidating the protein or by addition of surfactants. Proteins can be crosslinked prior to forming the microspheres. Other modifications can be made before or after formation of the microsphere, as long as the modification after formation does not have a detrimental effect on the incorporated compound.

Detailed Description Text (119):
Sprague-Dawley CD rats (Taconic Farms, N.Y.), weighing 175-225 g, were lightly anesthetized with methoxyflurane (Metafane, Pitman-Moore Inc., Washington Crossing, N.J.) and fed by gavage tube (20 in., 6 fr) with either 40-50 mg PLA/rhodamine microspheres or 20 mg Zein/rhodamine microspheres suspended in 1 ml isotonic saline. Rats were predosed with 60 mg of ranitidine by (p.o. Zantac.TM., Glaxo, Inc.) in 1 ml normal saline 3 hours prior to being fed the microspheres. Microsphere suspensions were sonicated for 2 minutes prior to feeding. Blood samples were taken via the tail vein at 30 minutes, 1 and 2 hours after introduction of the microspheres and collected in EDTA Microtainer tubes (Becton Dickinson, Paramus, N.J.).

Detailed Description Text (129):
Diabetes was induced in a Sprague Dawley rat (Taconics, Germantown, N.Y.) by injecting intravenously streptozotocin (Upjohn Co., Kalamazoo, Mich.) at a dose of 65 mg/kg in 0.1M citrate buffer pH 4.5. Two weeks after induction the rat was fed

by gayage the microspheres containing 17% w/w insulin as prepared in example 3 (120 mg in 2 ml of normal saline each morning for three days). Each day the animal was lightly anesthetized with Metofane (Pitman Moore Inc., Washington Crossing, N.J.) and 150 mg of Zantac.TM. (Glexco Inc.) in 2 ml of normal saline was fed to the animal via a 5 french gavage tube. Three hours after the Zantac.TM. administration, the animal was lightly anesthetized with Metofane and the microspheres were given to the animal using a 5 fr gavage tube. The blood glucose levels were monitored by sampling from the animal's tail vein and using a Glucometer II (Boerhinger Ingelheim) glucose meter. The animal's blood glucose profile is shown in FIG. 2.

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The probable cause is use of unlimited truncation. Revise your search strategy to use limited truncation.

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Search Results - Record(s) 1 through 5 of 5 returned.

☐ 1. Document ID: US RE35862 E

Using default format because multiple data bases are involved.

L2: Entry 1 of 5 File: USPT Jul 28, 1998

US-PAT-NO: RE35862
DOCUMENT-IDENTIFIER: US RE35862 E

TITLE: Delivery systems for pharmacological agents encapsulated with proteinoids

DATE-ISSUED: July 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon	Mt. Kisco	NY		
Rosen; Robert	Rochester	NY		

US-CL-CURRENT: 424/455; 264/4, 264/4.1, 424/451, 424/484

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 2. Document ID: US 5679377 A

L2: Entry 2 of 5 File: USPT Oct 21, 1997

US-PAT-NO: 5679377
DOCUMENT-IDENTIFIER: US 5679377 A
**** See image for Certificate of Correction ****

TITLE: Protein microspheres and methods of using them

DATE-ISSUED: October 21, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bernstein; Howard	Cambridge	MA		
Morrel; Eric	Needham	MA		

Mathiowitz; Edith	Brookline	MA
Schwaller; Kirsten	Duxbury	MA
Beck; Thomas R.	Concord	MA

US-CL-CURRENT: 424/491; 264/4.32, 264/4.6, 424/484, 424/485, 424/486, 427/2.14, 427/2.21, 427/213.31, 428/402.2, 428/402.21, 428/402.24, 514/866, 514/963, 514/965

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 3. Document ID: US 5271961 A

L2: Entry 3 of 5 File: USPT Dec 21, 1993

US-PAT-NO: 5271961
DOCUMENT-IDENTIFIER: US 5271961 A

TITLE: Method for producing protein microspheres

DATE-ISSUED: December 21, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Bernstein; Howard	Cambridge	MA		
Morrel; Eric	Needham	MA		
Schwaller; Kirsten	Duxbury	MA		

US-CL-CURRENT: 427/213.31; 424/491, 424/499, 426/96, 427/213.3, 427/213.36

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 4. Document ID: US 4925673 A

L2: Entry 4 of 5 File: USPT May 15, 1990

US-PAT-NO: 4925673
DOCUMENT-IDENTIFIER: US 4925673 A

TITLE: Delivery systems for pharmacological agents encapsulated with proteinoids

DATE-ISSUED: May 15, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon	Mt. Kisco	NY		
Rosen; Robert	Rochester	NY		

US-CL-CURRENT: 424/455; 264/4, 264/4.1, 424/451, 424/484

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 5. Document ID: US 20030129252 A1, WO 2003053414 A2

L2: Entry 5 of 5 File: DWPI Jul 10, 2003

DERWENT-ACC-NO: 2003-627277
DERWENT-WEEK: 200360

TITLE: Proteinoid microsphere useful for treatment of wounds comprises a mixture of amino acids that are thermally condensed and cross-linked with a cross linker that can form a pore upon exposure to a reducing agent

INVENTOR: QUIRK, S

PRIORITY-DATA: 2001US-0027441 (December 20, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20030129252 A1	July 10, 2003		000	A61K009/14
WO 2003053414 A2	July 3, 2003	E	022	A61K009/16

INT-CL (IPC): A61 K 9/14; A61 K 9/16; A61 K 9/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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Terms	Documents
L1 and cross$	5

Display Format: - Change Format

Previous Page Next Page Go to Doc#

Hit List

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 15 of 15 returned.

☐ 1. Document ID: US RE35862 E

Using default format because multiple data bases are involved.

L1: Entry 1 of 15 File: USPT Jul 28, 1998

US-PAT-NO: RE35862
DOCUMENT-IDENTIFIER: US RE35862 E

TITLE: Delivery systems for pharmacological agents encapsulated with proteinoids

DATE-ISSUED: July 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon	Mt. Kisco	NY		
Rosen; Robert	Rochester	NY		

US-CL-CURRENT: 424/455; 264/4, 264/4.1, 424/451, 424/484

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw. De

☐ 2. Document ID: US 5679377 A

L1: Entry 2 of 15 File: USPT Oct 21, 1997

US-PAT-NO: 5679377
DOCUMENT-IDENTIFIER: US 5679377 A
** See image for Certificate of Correction **

TITLE: Protein microspheres and methods of using them

DATE-ISSUED: October 21, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bernstein; Howard	Cambridge	MA		
Morrel; Eric	Needham	MA		
Mathiowitz; Edith	Brookline	MA		
Schwaller; Kirsten	Duxbury	MA		
Beck; Thomas R.	Concord	MA		

US-CL-CURRENT: 424/491; 264/4.32, 264/4.6, 424/484, 424/485, 424/486, 427/2.14, 427/2.21, 427/213.31, 428/402.2, 428/402.21, 428/402.24, 514/866, 514/963, 514/965

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 3. Document ID: US 5667806 A

L1: Entry 3 of 15 File: USPT Sep 16, 1997

US-PAT-NO: 5667806
DOCUMENT-IDENTIFIER: US 5667806 A

TITLE: Spray drying method and apparatus

DATE-ISSUED: September 16, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kantor; Martin L.	Mamaroneck	NY		

US-CL-CURRENT: 424/484; 264/4.1, 264/4.3, 264/4.33, 424/485, 424/486, 424/489, 424/490, 424/491, 424/497, 424/499

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 4. Document ID: US 5601846 A

L1: Entry 4 of 15 File: USPT Feb 11, 1997

US-PAT-NO: 5601846
DOCUMENT-IDENTIFIER: US 5601846 A

TITLE: Proteinoid microspheres and methods for preparation and use thereof

DATE-ISSUED: February 11, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Brooklyn	NY		
Kantor; Martin L.	Mamaroneck	NY		

US-CL-CURRENT: 424/499; 424/451, 424/469

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 5. Document ID: US 5443841 A

L1: Entry 5 of 15 File: USPT Aug 22, 1995

US-PAT-NO: 5443841

DOCUMENT-IDENTIFIER: US 5443841 A
**** See image for Certificate of Correction ****

TITLE: Proteinoid microspheres and methods for preparation and use thereof

DATE-ISSUED: August 22, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Brooklyn	NY		
Kantor; Martin L.	Mamaroneck	NY		

US-CL-CURRENT: 424/451; 424/491

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 6. Document ID: US 5271961 A

L1: Entry 6 of 15 File: USPT Dec 21, 1993

US-PAT-NO: 5271961
DOCUMENT-IDENTIFIER: US 5271961 A

TITLE: Method for producing protein microspheres

DATE-ISSUED: December 21, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Bernstein; Howard	Cambridge	MA		
Morrel; Eric	Needham	MA		
Schwaller; Kirsten	Duxbury	MA		

US-CL-CURRENT: 427/213.31; 424/491, 424/499, 426/96, 427/213.3, 427/213.36

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 7. Document ID: US 4983402 A

L1: Entry 7 of 15 File: USPT Jan 8, 1991

US-PAT-NO: 4983402
DOCUMENT-IDENTIFIER: US 4983402 A

TITLE: Orally administerable ANF

DATE-ISSUED: January 8, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon S.	Mt. Kisco	NY		

US-CL-CURRENT: 424/491; 424/455

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. De

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☐ 8. Document ID: US 4976968 A

L1: Entry 8 of 15 File: USPT Dec 11, 1990

US-PAT-NO: 4976968
DOCUMENT-IDENTIFIER: US 4976968 A

TITLE: Anhydrous delivery systems for pharmacological agents

DATE-ISSUED: December 11, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon S.	Mt. Kisco	NY		

US-CL-CURRENT: 424/491; 424/455

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. De

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☐ 9. Document ID: US 4925673 A

L1: Entry 9 of 15 File: USPT May 15, 1990

US-PAT-NO: 4925673
DOCUMENT-IDENTIFIER: US 4925673 A

TITLE: Delivery systems for pharmacological agents encapsulated with proteinoids

DATE-ISSUED: May 15, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon	Mt. Kisco	NY		
Rosen; Robert	Rochester	NY		

US-CL-CURRENT: 424/455; 264/4, 264/4.1, 424/451, 424/484

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. De

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☐ 10. Document ID: US 4381990 A

L1: Entry 10 of 15 File: USPT May 3, 1983

US-PAT-NO: 4381990
DOCUMENT-IDENTIFIER: US 4381990 A

TITLE: Process for producing mesocarbon microbeads of uniform particle-size distribution

DATE-ISSUED: May 3, 1983

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Noguchi; Kosaku	Tokyo			JP
Tanaka; Honami	Izumi			JP
Kumura; Yukimasa	Izumi			JP
Kitajima; Eiji	Izumi			JP
Tsuchiya; Noriyuki	Izumi			JP
Sunada; Tomonori	Ootsu			JP

US-CL-CURRENT: 208/39; 208/45

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 11. Document ID: US 20030129252 A1, WO 2003053414 A2

L1: Entry 11 of 15 File: DWPI Jul 10, 2003

DERWENT-ACC-NO: 2003-627277
DERWENT-WEEK: 200360
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Proteinoid microsphere useful for treatment of wounds comprises a mixture of amino acids that are thermally condensed and cross-linked with a cross linker that can form a pore upon exposure to a reducing agent

INVENTOR: QUIRK, S

PRIORITY-DATA: 2001US-0027441 (December 20, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20030129252 A1	July 10, 2003		000	A61K009/14
WO 2003053414 A2	July 3, 2003	E	022	A61K009/16

INT-CL (IPC): A61 K 9/14; A61 K 9/16; A61 K 9/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 12. Document ID: CN 1259546 A

L1: Entry 12 of 15 File: DWPI Jul 12, 2000

DERWENT-ACC-NO: 2000-572894

DERWENT-WEEK: 200054
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Preparation method of mesophase asphalt carbon microsphere

INVENTOR: CHEN, X; SHEN, Z ; SONG, H

PRIORITY-DATA: 1999CN-0100008 (January 4, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
CN 1259546 A	July 12, 2000		000	C08L095/00

INT-CL (IPC): C08 L 95/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 13. Document ID: US 4983402 A

L1: Entry 13 of 15 File: DWPI Jan 8, 1991

DERWENT-ACC-NO: 1991-036189
DERWENT-WEEK: 199105
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TITLE: Orally administrable atrial natriuretic factor compsn. - encapsulated in acidic proteinoid microspheres formed from thermal condensation polymers of mixed aminoacid(s)

INVENTOR: STEINER, S S

PRIORITY-DATA: 1989US-0315393 (February 24, 1989)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 4983402 A	January 8, 1991		000	

INT-CL (IPC): A61K 9/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 14. Document ID: US 4976968 A

L1: Entry 14 of 15 File: DWPI Dec 11, 1990

DERWENT-ACC-NO: 1991-006674
DERWENT-WEEK: 199101
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Anhydrous pharmacological agent - is encapsulated in protein microspheres for targetted delivery of agent to e.g. gastrointestinal tract

INVENTOR: STEINER, S S

PRIORITY-DATA: 1989US-0315440 (February 24, 1989)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 4976968 A	December 11, 1990		000	

INT-CL (IPC): A61K 9/50

☐ 15. Document ID: WO 8801213 A, JP 2876058 B2, AU 8778752 A, NO 8801664 A, DK 8802059 A, NL 8720442 A, EP 318512 A, DE 3790487 T, CH 671155 A, FI 8900782 A, GB 2217201 A, SE 8900542 A, PT 86571 A, ES 2008964 A, JP 02500669 W, US 4925673 A, CN 1034858 A, HU 52947 T, GB 2217201 B, IL 84935 A, AU 9187886 A, HU 207439 B, EP 545913 A1, CA 1323305 C, DE 3745075 A1, DE 3790487 C2, NO 178055 B, SE 502324 B, DE 3745075 C1, EP 318512 B1, US 35862 E, KR 9509089 B1, FI 102456 B1, EP 545913 B1

L1: Entry 15 of 15 File: DWPI Feb 25, 1988

DERWENT-ACC-NO: 1988-063948
DERWENT-WEEK: 199918

TITLE: Therapeutic agent encapsulated in proteinoid microspheres - for oral admin. to protect agent against gastrointestinal tract deactivation

INVENTOR: ROSEN, R; STEINER, S S ; STEINER, S

PRIORITY-DATA: 1986US-0897361 (August 18, 1986), 1988ES-0000260 (January 29, 1988), 1987US-0098027 (August 14, 1987), 1987CA-0554255 (December 14, 1987), 1992US-0883562 (May 15, 1992), 1994US-0252979 (June 2, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 8801213 A	February 25, 1988	E	032	
JP 2876058 B2	March 31, 1999		009	A61K009/50
AU 8778752 A	March 8, 1988		000	
NO 8801664 A	July 4, 1988		000	
DK 8802059 A	May 31, 1988		000	
NL 8720442 A	April 3, 1989		000	
EP 318512 A	June 7, 1989	E	000	
DE 3790487 T	July 6, 1989		000	
CH 671155 A	August 15, 1989		000	
FI 8900782 A	February 17, 1989		000	
GB 2217201 A	October 25, 1989		000	
SE 8900542 A	February 16, 1989		000	
PT 86571 A	October 4, 1989		000	
ES 2008964 A	August 16, 1989		000	
JP 02500669 W	March 8, 1990		000	
US 4925673 A	May 15, 1990		009	
CN 1034858 A	August 23, 1989		000	
HU 52947 T	September 28, 1990		000	
GB 2217201 B	January 23, 1991		000	

IL 84935 A	January 15, 1992		000	
AU 9187886 A	January 16, 1992		000	
HU 207439 B	April 28, 1993		000	A61K009/64
EP 545913 A1	June 9, 1993	E	016	A61K009/16
CA 1323305 C	October 19, 1993		000	A61K009/50
DE 3745075 A1	March 17, 1994		000	A61K009/64
DE 3790487 C2	August 18, 1994		012	A61K009/64
NO 178055 B	October 9, 1995		000	A61K009/50
SE 502324 B	October 2, 1995		000	A61K009/16
DE 3745075 C1	April 30, 1997		012	A61K009/64
EP 318512 B1	June 17, 1998	E	000	B23B005/16
US 35862 E	July 28, 1998		000	A61K009/66
KR 9509089 B1	August 14, 1995		000	A61K009/50
FI 102456 B1	December 15, 1998		000	A61K009/50
EP 545913 B1	February 24, 1999	E	000	A61K009/16

1034858 A INT-CL (IPC): A01N 25/26; A61J 5/04; A61K 9/16; A61K 9/50; A61K 9/52; A61K 9/64; A61K 9/66; A61K 31/40; A61K 31/72; A61K 31/725; A61K 37/26; A61K 38/28; A61K 47/42; B01J 13/02; B23B 5/16; B23B 9/02; B23B 9/04; C07K 15/00

Terms	Documents
microsphere$ same (thermal$ adj2 condens$)	15

Hit List

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Search Results - Record(s) 1 through 15 of 15 returned.

☐ 1. Document ID: US RE35862 E

Using default format because multiple data bases are involved.

L1: Entry 1 of 15 File: USPT Jul 28, 1998

US-PAT-NO: RE35862
DOCUMENT-IDENTIFIER: US RE35862 E

TITLE: Delivery systems for pharmacological agents encapsulated with proteinoids

DATE-ISSUED: July 28, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon	Mt. Kisco	NY		
Rosen; Robert	Rochester	NY		

US-CL-CURRENT: 424/455; 264/4, 264/4.1, 424/451, 424/484

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 2. Document ID: US 5679377 A

L1: Entry 2 of 15 File: USPT Oct 21, 1997

US-PAT-NO: 5679377
DOCUMENT-IDENTIFIER: US 5679377 A
** See image for Certificate of Correction **

TITLE: Protein microspheres and methods of using them

DATE-ISSUED: October 21, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bernstein; Howard	Cambridge	MA		
Morrel; Eric	Needham	MA		
Mathiowitz; Edith	Brookline	MA		
Schwaller; Kirsten	Duxbury	MA		
Beck; Thomas R.	Concord	MA		

US-CL-CURRENT: 424/491; 264/4.32, 264/4.6, 424/484, 424/485, 424/486, 427/2.14, 427/2.21, 427/213.31, 428/402.2, 428/402.21, 428/402.24, 514/866, 514/963, 514/965

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 3. Document ID: US 5667806 A

L1: Entry 3 of 15 File: USPT Sep 16, 1997

US-PAT-NO: 5667806
DOCUMENT-IDENTIFIER: US 5667806 A

TITLE: Spray drying method and apparatus

DATE-ISSUED: September 16, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kantor; Martin L.	Mamaroneck	NY		

US-CL-CURRENT: 424/484; 264/4.1, 264/4.3, 264/4.33, 424/485, 424/486, 424/489, 424/490, 424/491, 424/497, 424/499

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 4. Document ID: US 5601846 A

L1: Entry 4 of 15 File: USPT Feb 11, 1997

US-PAT-NO: 5601846
DOCUMENT-IDENTIFIER: US 5601846 A

TITLE: Proteinoid microspheres and methods for preparation and use thereof

DATE-ISSUED: February 11, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Brooklyn	NY		
Kantor; Martin L.	Mamaroneck	NY		

US-CL-CURRENT: 424/499; 424/451, 424/469

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 5. Document ID: US 5443841 A

L1: Entry 5 of 15 File: USPT Aug 22, 1995

US-PAT-NO: 5443841

DOCUMENT-IDENTIFIER: US 5443841 A
**** See image for Certificate of Correction ****

TITLE: Proteinoid microspheres and methods for preparation and use thereof

DATE-ISSUED: August 22, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Brooklyn	NY		
Kantor; Martin L.	Mamaroneck	NY		

US-CL-CURRENT: 424/451; 424/491

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 6. Document ID: US 5271961 A

L1: Entry 6 of 15 File: USPT Dec 21, 1993

US-PAT-NO: 5271961
DOCUMENT-IDENTIFIER: US 5271961 A

TITLE: Method for producing protein microspheres

DATE-ISSUED: December 21, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mathiowitz; Edith	Brookline	MA		
Bernstein; Howard	Cambridge	MA		
Morrel; Eric	Needham	MA		
Schwaller; Kirsten	Duxbury	MA		

US-CL-CURRENT: 427/213.31; 424/491, 424/499, 426/96, 427/213.3, 427/213.36

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 7. Document ID: US 4983402 A

L1: Entry 7 of 15 File: USPT Jan 8, 1991

US-PAT-NO: 4983402
DOCUMENT-IDENTIFIER: US 4983402 A

TITLE: Orally administerable ANF

DATE-ISSUED: January 8, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon S.	Mt. Kisco	NY		

US-CL-CURRENT: 424/491; 424/455

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw. De

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☐ 8. Document ID: US 4976968 A

L1: Entry 8 of 15 File: USPT Dec 11, 1990

US-PAT-NO: 4976968
DOCUMENT-IDENTIFIER: US 4976968 A

TITLE: Anhydrous delivery systems for pharmacological agents

DATE-ISSUED: December 11, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon S.	Mt. Kisco	NY		

US-CL-CURRENT: 424/491; 424/455

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw. De

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☐ 9. Document ID: US 4925673 A

L1: Entry 9 of 15 File: USPT May 15, 1990

US-PAT-NO: 4925673
DOCUMENT-IDENTIFIER: US 4925673 A

TITLE: Delivery systems for pharmacological agents encapsulated with proteinoids

DATE-ISSUED: May 15, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Steiner; Solomon	Mt. Kisco	NY		
Rosen; Robert	Rochester	NY		

US-CL-CURRENT: 424/455; 264/4, 264/4.1, 424/451, 424/484

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWMC | Draw. De

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☐ 10. Document ID: US 4381990 A

L1: Entry 10 of 15 File: USPT May 3, 1983

US-PAT-NO: 4381990
DOCUMENT-IDENTIFIER: US 4381990 A

TITLE: Process for producing mesocarbon microbeads of uniform particle-size distribution

DATE-ISSUED: May 3, 1983

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Noguchi; Kosaku	Tokyo			JP
Tanaka; Honami	Izumi			JP
Kumura; Yukimasa	Izumi			JP
Kitajima; Eiji	Izumi			JP
Tsuchiya; Noriyuki	Izumi			JP
Sunada; Tomonori	Ootsu			JP

US-CL-CURRENT: 208/39; 208/45

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 11. Document ID: US 20030129252 A1, WO 2003053414 A2

L1: Entry 11 of 15 File: DWPI Jul 10, 2003

DERWENT-ACC-NO: 2003-627277
DERWENT-WEEK: 200360
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Proteinoid microsphere useful for treatment of wounds comprises a mixture of amino acids that are thermally condensed and cross-linked with a cross linker that can form a pore upon exposure to a reducing agent

INVENTOR: QUIRK, S

PRIORITY-DATA: 2001US-0027441 (December 20, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20030129252 A1	July 10, 2003		000	A61K009/14
WO 2003053414 A2	July 3, 2003	E	022	A61K009/16

INT-CL (IPC): A61 K 9/14; A61 K 9/16; A61 K 9/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 12. Document ID: CN 1259546 A

L1: Entry 12 of 15 File: DWPI Jul 12, 2000

DERWENT-ACC-NO: 2000-572894

DERWENT-WEEK: 200054
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Preparation method of mesophase asphalt carbon microsphere

INVENTOR: CHEN, X; SHEN, Z ; SONG, H

PRIORITY-DATA: 1999CN-0100008 (January 4, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
CN 1259546 A	July 12, 2000		000	C08L095/00

INT-CL (IPC): C08 L 95/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 13. Document ID: US 4983402 A

L1: Entry 13 of 15 File: DWPI Jan 8, 1991

DERWENT-ACC-NO: 1991-036189
DERWENT-WEEK: 199105
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Orally administrable atrial natriuretic factor compsn. - encapsulated in acidic proteinoid microspheres formed from thermal condensation polymers of mixed aminoacid(s)

INVENTOR: STEINER, S S

PRIORITY-DATA: 1989US-0315393 (February 24, 1989)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 4983402 A	January 8, 1991		000	

INT-CL (IPC): A61K 9/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 14. Document ID: US 4976968 A

L1: Entry 14 of 15 File: DWPI Dec 11, 1990

DERWENT-ACC-NO: 1991-006674
DERWENT-WEEK: 199101
COPYRIGHT 2004 DERWENT INFORMATION LTD
TITLE: Anhydrous pharmacological agent - is encapsulated in protein microspheres for targetted delivery of agent to e.g. gastrointestinal tract

INVENTOR: STEINER, S S

PRIORITY-DATA: 1989US-0315440 (February 24, 1989)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 4976968 A	December 11, 1990		000	

INT-CL (IPC): A61K 9/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 15. Document ID: WO 8801213 A, JP 2876058 B2, AU 8778752 A, NO 8801664 A, DK 8802059 A, NL 8720442 A, EP 318512 A, DE 3790487 T, CH 671155 A, FI 8900782 A, GB 2217201 A, SE 8900542 A, PT 86571 A, ES 2008964 A, JP 02500669 W, US 4925673 A, CN 1034858 A, HU 52947 T, GB 2217201 B, IL 84935 A, AU 9187886 A, HU 207439 B, EP 545913 A1, CA 1323305 C, DE 3745075 A1, DE 3790487 C2, NO 178055 B, SE 502324 B, DE 3745075 C1, EP 318512 B1, US 35862 E, KR 9509089 B1, FI 102456 B1, EP 545913 B1

L1: Entry 15 of 15 File: DWPI Feb 25, 1988

DERWENT-ACC-NO: 1988-063948
DERWENT-WEEK: 199918

TITLE: Therapeutic agent encapsulated in proteinoid microspheres - for oral admin. to protect agent against gastrointestinal tract deactivation

INVENTOR: ROSEN, R; STEINER, S S ; STEINER, S

PRIORITY-DATA: 1986US-0897361 (August 18, 1986), 1988ES-0000260 (January 29, 1988), 1987US-0098027 (August 14, 1987), 1987CA-0554255 (December 14, 1987), 1992US-0883562 (May 15, 1992), 1994US-0252979 (June 2, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 8801213 A	February 25, 1988	E	032	
JP 2876058 B2	March 31, 1999		009	A61K009/50
AU 8778752 A	March 8, 1988		000	
NO 8801664 A	July 4, 1988		000	
DK 8802059 A	May 31, 1988		000	
NL 8720442 A	April 3, 1989		000	
EP 318512 A	June 7, 1989	E	000	
DE 3790487 T	July 6, 1989		000	
CH 671155 A	August 15, 1989		000	
FI 8900782 A	February 17, 1989		000	
GB 2217201 A	October 25, 1989		000	
SE 8900542 A	February 16, 1989		000	
PT 86571 A	October 4, 1989		000	
ES 2008964 A	August 16, 1989		000	
JP 02500669 W	March 8, 1990		000	
US 4925673 A	May 15, 1990		009	
CN 1034858 A	August 23, 1989		000	
HU 52947 T	September 28, 1990		000	
GB 2217201 B	January 23, 1991		000	

IL 84935 A	January 15, 1992		000	
AU 9187886 A	January 16, 1992		000	
HU 207439 B	April 28, 1993		000	A61K009/64
EP 545913 A1	June 9, 1993	E	016	A61K009/16
CA 1323305 C	October 19, 1993		000	A61K009/50
DE 3745075 A1	March 17, 1994		000	A61K009/64
DE 3790487 C2	August 18, 1994		012	A61K009/64
NO 178055 B	October 9, 1995		000	A61K009/50
SE 502324 B	October 2, 1995		000	A61K009/16
DE 3745075 C1	April 30, 1997		012	A61K009/64
EP 318512 B1	June 17, 1998	E	000	B23B005/16
US 35862 E	July 28, 1998		000	A61K009/66
KR 9509089 B1	August 14, 1995		000	A61K009/50
FI 102456 B1	December 15, 1998		000	A61K009/50
EP 545913 B1	February 24, 1999	E	000	A61K009/16

1034858 A INT-CL (IPC): A01N 25/26; A61J 5/04; A61K 9/16; A61K 9/50; A61K 9/52; A61K 9/64; A61K 9/66; A61K 31/40; A61K 31/72; A61K 31/725; A61K 37/26; A61K 38/28; A61K 47/42; B01J 13/02; B23B 5/16; B23B 9/02; B23B 9/04; C07K 15/00

Terms	Documents
microsphere$ same (thermal$ adj2 condens$)	15

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L3: Entry 1 of 3 File: USPT Apr 4, 1995

DOCUMENT-IDENTIFIER: US 5403573 A
TITLE: Radiolabeled protein composition and method for radiation synovectomy

Abstract Text (1):
A radiolabeled protein composition adapted for radiation therapy which comprises a radioisotope and a protein material containing about 6 or more percent amino acids which have a sulfhydryl-containing side chain. A method for carrying out radiation synovectomy of arthritic joints. Rhenium radiolabeled protein microspheres are administered which contain cysteine and other amino acids. A method for radiolabeling a protein composition whereby the composition is treated with a reducing agent capable of reducing disulfides to sulfhydryls prior to radiolabeling.

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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 5403573 A

Using default format because multiple data bases are involved.

L3: Entry 1 of 3 File: USPT Apr 4, 1995

US-PAT-NO: 5403573
DOCUMENT-IDENTIFIER: US 5403573 A

TITLE: Radiolabeled protein composition and method for radiation synovectomy

DATE-ISSUED: April 4, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Day; Delbert E.	Rolla	MO		
Ehrhardt; Gary J.	Columbia	MO		
Zinn; Kurt R.	Columbia	MO		

US-CL-CURRENT: 424/1.29; 424/1.37, 424/1.49, 424/1.69

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 2. Document ID: JP 63207382 A

L3: Entry 2 of 3 File: JPAB Aug 26, 1988

PUB-NO: JP363207382A
DOCUMENT-IDENTIFIER: JP 63207382 A
TITLE: PRODUCTION OF CARRIER FOR CELL CULTURE

PUBN-DATE: August 26, 1988

INVENTOR-INFORMATION:

NAME	COUNTRY
YASUDA, KENJI	
TAI, SEIJI	
KITAJIMA, MASAAKI	
KANAYAMA, HISANORI	

US-CL-CURRENT: 435/182

INT-CL (IPC): C12N 5/02; C12M 3/02

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 3. Document ID: US 20030129252 A1, WO 2003053414 A2

L3: Entry 3 of 3 File: DWPI Jul 10, 2003

DERWENT-ACC-NO: 2003-627277
DERWENT-WEEK: 200360

TITLE: Proteinoid microsphere useful for treatment of wounds comprises a mixture of amino acids that are thermally condensed and cross-linked with a cross linker that can form a pore upon exposure to a reducing agent

INVENTOR: QUIRK, S

PRIORITY-DATA: 2001US-0027441 (December 20, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20030129252 A1	July 10, 2003		000	A61K009/14
WO 2003053414 A2	July 3, 2003	E	022	A61K009/16

INT-CL (IPC): A61 K 9/14; A61 K 9/16; A61 K 9/50

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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Terms	Documents
L1 same (reducing adj2 agent$)	3

Display Format: - Change Format

Previous Page Next Page Go to Doc#

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L2: Entry 12 of 57 File: USPT Oct 8, 2002

DOCUMENT-IDENTIFIER: US 6461643 B2
TITLE: Oral drug delivery compositions and methods

Brief Summary Text (6):
More recently, microspheres of artificial polymers or proteinoids of mixed amino acids have been described for delivery of pharmaceuticals. For example, U.S. Pat. No. 4,925,673 describes drug containing microsphere constructs as well as methods for their preparation and use. These proteinoid microspheres are useful for delivery of a number of active agents.

Detailed Description Text (18):
The amino acid derivatives or peptide derivatives of the present invention can be readily prepared by reduction of amino acid esters or peptide esters with an appropriate reducing agent. For example, amino acid aldehydes or peptide aldehydes can be prepared as described in an article by R. Chen et al., Biochemistry, 1979, 18, 921-926. Amino acid or peptide ketones can be prepared by the procedure described in Organic Syntheses, Col. Vol. IV, Wiley, (1963), pages 5-6. Amino acids, peptides, amino acid esters, peptide esters, and other necessary reagents to prepare these derivatives are readily available from a number of commercial sources such as Aldrich Chemical Co. (Milwaukee, Wis., USA); Sigma Chemical Co. (St. Louis, Mo., USA); and Fluka Chemical Corp. (Ronkonkoma, N.Y., USA).

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L2: Entry 28 of 57 File: USPT Feb 27, 2001

DOCUMENT-IDENTIFIER: US 6193953 B1
TITLE: Stabilized microparticles and their use as ultrasound contrast agents

Brief Summary Text (7):
Generally, microparticles of a particular gas in the form of protein-shelled microspheres exhibit improved in vivo stability when compared to free bubbles of the same gas. However, most protein-shelled microspheres still have relatively short in vivo half lives which compromise their usefulness as contrast agents. This instability in vivo was thought to result from the collapse or breakdown of the protein shells under pressure resulting in rapid diffusion of the gas from the microspheres. Thus, many recent efforts have centered on improvements to the protein shell as a way of increasing in vivo pressure stability, such as coating the protein shell with surfactants (Giddy, WO 92/05806), binding the protein with a protein-reactive aldehyde (Feinstein et al., U.S. Pat. No. 4,718,433 and U.S. Pat. No. 4,774,958), covalently cross-linking the protein shell (Holmes et al., WO 92/17213) and ionically cross-linking the protein shell (Klaveness et al., WO 95/23615).

Detailed Description Text (46):
It is also possible to utilize the existing disulfide groups on the surface of the tanned microparticles as a site of attachment of functional groups. As shown in Reaction 2 of FIG. 3, the disulfide bonds are reduced using typical reducing agents, such as 2-mercaptoethanol or dithiothreitol. A preferred reducing agent is tris-(2-carboxyethyl) phosgene (TCEP). Chromium treated microparticles are stable during the reduction process. Excess reducing agent is removed, and the resultant microparticles are washed in the absence of oxygen. The resultant thiol groups are capable of participating in hydro-alkylthio-additions with alkene or alkyne groups. For example, vinylsulfone or maleimido groups (R.sub.1) are known to be very selective for reactions with sulfhydryls at very mild conditions at pH 7. Vinylsulfone is preferable over maleimide because of its greater hydrolytic stability in water. Such stability has a distinct advantage over active ester modified PEG, which is susceptible to hydrolysis under attachment conditions. Accordingly, the vinylsulfone derivatized PEG-peptide conjugate (R.sub.1 -PEG-T) can be efficiently attached to the microparticle surface via a very stable thioether linkage (Reaction 2 of FIG. 3.) After the attachment procedure is over, the unreacted thiol groups are oxidized to form disulfide bonds under mild oxidative conditions. Vinylsulfone groups have the additional advantage to undergo hydro-amino additions. Thus, a vinylsulfone group will react slowly with amine groups at pH 9-11 (Reaction 3 of FIG. 3.) This allows the R.sub.1 -PEG-T to not only attach to the thiol groups, but also to some extent to amino groups. This can enable conjugation of two different vinylsulfone-activated functional moieties, one which reacts at neutral pH and attaches to the thiol groups and another which reacts at higher pH and attaches to the amino groups.

L3: Entry 1 of 7 File: USPT Apr 1, 2003

DOCUMENT-IDENTIFIER: US 6541606 B2
TITLE: Stabilized protein crystals formulations containing them and methods of making them

Detailed Description Text (125):
Protein crystal formulation--a combination of protein crystals encapsulated within a polymeric carrier to form coated particles. The coated particles of the protein crystal formulation may have a spherical morphology and be microspheres of up to 500 micro meters in diameter or they may have some other morphology and be microparticulates. For the purposes of this application, "protein crystal formulations" are included in the term "compositions".

Detailed Description Text (127):
Protein loading--the protein content of microspheres, as calculated as a percentage by weight of protein relative to the weight of the dry formulation. A typical range of protein loading is from 1-80%.

Detailed Description Text (145):
Those of skill in the art will appreciate that protein stability is one of the most important obstacles to successful formulation of polymer microparticulate delivery systems that control the release of proteins. The stability of proteins encapsulated in polymeric carriers may be challenged at three separate stages: manufacture of the protein crystal composition, protein release from the resulting composition and in vivo stability after the protein release. During preparation of microparticles or microspheres containing soluble or amorphous proteins, the use of organic solvents and lyophilization are especially detrimental to protein stability. Subsequently, released proteins are susceptible to moisture-induced aggregation, thus resulting in permanent inactivation.

Detailed Description Text (176):
Pharmaceutical, personal care, veterinary or prophylactic formulations and compositions comprising protein or nucleic acid crystal or crystal formulations or compositions according to this invention may also be selected from the group consisting of tablets, liposomes, granules, spheres, microparticles, microspheres and capsules.

Detailed Description Text (190):
Other formulations and compositions according to this invention include vaccine formulations and compositions comprising protein (antigen) crystals, adjuvant and encapsulating polymer(s). The protein antigen may be a viral glycoprotein, viral structural protein, viral enzyme, bacterial protein, or some engineered homolog of a viral or bacterial protein, or any immunopotentiating protein, such as a cytokine. One embodiment of such formulations or compositions involves a single vaccine injection containing microspheres having three or more different release profiles. In this way, antigen formulations or composition may be released over a sustained period sufficient to generate lasting immunity. By virtue of this formulation or composition, multiple antigen boosts may be in single unit form. The faster degrading preparation (composition) may contain an immunogenic adjuvant to enhance the immune response. One advantage of such a system is that by using protein crystals, the native three-dimensional structures of the epitopes are

maintained and presented to the immune system in their native form.

Detailed Description Text (191):
Once the immune system is primed, there may be less need for an adjuvant effect. Therefore, in the slower degrading inoculations, a less immunogenic adjuvant may be included and possibly no adjuvant may be required in the slowest degrading microspheres of the formulations and compositions . In this way, patient populations in remote areas will not have to be treated multiple times in order to provide protection against infectious diseases. One of skill in the art of biological delivery of proteins will appreciate that many variations on this theme are feasible. Accordingly, the examples provided here are not intended to limit the invention.

Detailed Description Text (192):
In another embodiment of this invention, a combination vaccine could be produced, whereby immunity to multiple diseases is induced in a single injection. As discussed above, microspheres having different release profiles may be combined alone or in formulations and compositions and may include microspheres containing antigens from multiple infectious agents to produce a combination vaccine (formulations and compositions). For example, microspheres having multiple release profiles and containing antigen crystals of measles, mumps, rubella, polio and hepatitis B agents could be combined and administered to children. Alternatively, microspheres having multiple release profiles and containing crystals of different isolates of HIV gp120 could be combined to produce a vaccine for HIV-1 or HIV-2.

Detailed Description Text (193):
Another advantage of the present invention is that the protein crystals encapsulated within polymeric carriers and forming a composition comprising microspheres can be dried by lyophilization. Lyophilization, or freeze-drying allows water to be separated from the composition. The protein crystal composition is first frozen and then placed in a high vacuum. In a vacuum, the crystalline H.sub.2 O sublimes, leaving the protein crystal composition behind containing only the tightly bound water. Such processing further stabilizes the composition and allows for easier storage and transportation at typically encountered ambient temperatures.

Detailed Description Text (220):
Disulfide crosslinkers are described in the Pierce Catalog and Handbook (1994-1995) and more recently in "Bioconjugate Techniques", By G. T. Hermanson, (1996), Academic Press, Division of Harcourt Brace & Company, 525 B Street, Suite 1900, San Diego, Calif. 92101-4495.

Detailed Description Text (227):
According to one embodiment of this invention, compositions are produced when protein crystals are encapsulated in at least one polymeric carrier to form microspheres by virtue of encapsulation within the matrix of the polymeric carrier to preserve their native and biologically active tertiary structure. The crystals can be encapsulated using various biocompatible and/or biodegradable polymers having unique properties which are suitable for delivery to different biological environments or for effecting specific functions. The rate of dissolution and, therefore, delivery of active protein is determined by the particular encapsulation technique, polymer composition, polymer crosslinking, polymer thickness, polymer solubility, protein crystal geometry and degree and, if any, of protein crystal crosslinking

Detailed Description Text (229):
Following that contact, the crystals become coated and are referred to as nascent microspheres. The nascent microspheres increase in size while coating occurs. In a preferred embodiment of the invention, the suspended coated crystals or nascent microspheres along with the polymeric carrier and organic solvent are transferred

to a larger volume of an aqueous solution containing a surface active agent, known as an emulsifier. In the aqueous solution, the suspended nascent microspheres are immersed in the aqueous phase, where the organic solvent evaporates or diffuses away from the polymer. Eventually, a point is reached where the polymer is no longer soluble and forms a precipitated phase encapsulating the protein crystals or formulations to form a composition. This aspect of the process is referred to as hardening of the polymeric carrier or polymer. The emulsifier helps to reduce the interfacial surface tension between the various phases of matter in the system during the hardening phase of the process. Alternatively, if the coating polymer has some inherent surface activity, there may be no need for addition of a separate surface active agent.

Detailed Description Text (231):
Organic solvents useful to prepare the microspheres of the present invention include methylene chloride, ethyl acetate, chloroform and other non-toxic solvents which will depend on the properties of the polymer. Solvents should be chosen that solubilize the polymer and are ultimately non-toxic.

Detailed Description Text (233):
The polymers used as polymeric carriers to coat the protein crystals can be either homo-polymers or co-polymers. The rate of hydrolysis of the microspheres is largely determined by the hydrolysis rate of the individual polymer species. In general, the rate of hydrolysis decreases as follows:
polycarbonates>polyesters>polyurethanes>polyorthoesters> polyamides. For a review of biodegradable and biocompatible polymers, see W. R. Gombotz and D. K. Pettit, "Biodegradable polymers for protein and peptide drug delivery", Bioconjugate Chemistry, vol. 6, pp. 332-351 (1995).

Detailed Description Text (237):
In another embodiment, double-walled polymer coated microspheres may be advantageous. Double-walled polymer coated microspheres may be produced by preparing two separate polymer solutions in methylene chloride or other solvent which can dissolve the polymers. The protein crystals are added to one of the solutions and dispersed. Here, the protein crystals become coated with the first polymer. Then, the solution containing the first polymer coated protein crystals is combined with the second polymer solution. [See Pekarek, K. J.; Jacob, J. S. and Mathiowitz, E. Double-walled polymer microspheres for controlled drug release, Nature, 367, 258-260]. Now, the second polymer encapsulates the first polymer which is encapsulating the protein crystal. Ideally, this solution is then dripped into a larger volume of an aqueous solution containing a surface active agent or emulsifier. In the aqueous solution, the solvent evaporates from the two polymer solutions and the polymers are precipitated.

Detailed Description Text (518):
Microencapsulation was performed using uncrosslinked crystals of lipase from Candida rugosa and Pseudomonas cepacia, glucose oxidase from Aspergillus niger and Penicillin acylase from Escherichia coli. Further, microencapsulation was performed using crosslinked enzyme crystals of lipase from Candida rugosa, glucose oxidase from Aspergillus niger and Penicillin acylase from Escherichia coli. Table 13 shows the approximate average diameters of samples of the microspheres which were produced by this example. In addition, human serum albumin or any other protein crystals or protein crystal formulation produced may be encapsulated by this technique.

Detailed Description Text (520):
Crystals or crystal formulations dried according to Example 6 may each be used to produce the microspheres of this invention. One process for drying protein crystals for use in this invention involves air drying.

Detailed Description Text (526):

The crystals were encapsulated in PLGA using a double emulsion method. The general process was as follows, either dry protein crystals or a slurry of protein crystals was first added to a polymer solution in methylene chloride. The crystals were coated with the polymer and became nascent microspheres. Next, the polymer in organic solvent solution was transferred to a much larger volume of an aqueous solution containing a surface active agent. As a result, the organic solvent began to evaporate and the polymer hardened. In this example, two successive aqueous solutions of decreasing concentrations of emulsifier were employed for hardening of the polymer coat to form microspheres. The following procedure was one exemplification of this general process. Those of skill in the art of polymer science will appreciate that many variations of the procedure may be employed and the following example was not meant to limit the invention.

Detailed Description Text (528):
Dry crystals of crosslinked and uncrosslinked Candida rugosa lipase produced according to Example 1, crosslinked and uncrosslinked glucose oxidase produced according to Examples 21 and 45, crosslinked and uncrosslinked penicillin acylase produced according to Example 14 and 47, were weighed into 150 mg samples. The weighed protein crystals were then added directly into a 15 ml polypropylene centrifuge tube (Fisher Scientific) containing 2 ml of methylene chloride with PLGA at 0.6 g PLGA/ml solvent. The crystals were added directly to the surface of the solvent. Next, the tube was throughly mixed by vortexing for 2 minutes at room temperature to completely disperse the protein crystals in the solvent with PLGA. The crystals were allowed to become completely coated with polymer. Further vortexing or agitation may be used to keep the nascent microspheres suspended to allow further coating. The polymer may be hardened as described in section 3.0.

Detailed Description Text (530):
A crystal slurry of Pseudomonas cepacia lipase was produced using approximately 50 mg of crystals per 200 .mu.l of mother liquor. The crystal slurry was rapidly injected into a 15 ml polypropylene centrifuge tube (Fisher Scientific) with 2 ml of a solution of methylene chloride and poly(lactic-co-glycolic acid) at 0.6 g PLGA/ml solvent. The needle was inserted below the surface of the solvent and injected into the solution. In this case, 150 mg of total protein, or 600 .mu.l of aqueous solution, was injected. The injection was made using a plastic syringe Leur-lok (Becton-Dickinson & Company) and through a 22 gauge (Becton-Dickinson & Company) stainless steel needle. Next, the protein crystal-PLGA slurry was mixed thoroughly by vortexing for 2 minutes at room temperature. The crystals were allowed to be completely coated with polymer. Further vortexing or agitation was optionally used to keep the nascent microspheres suspended to allow further coating.

Detailed Description Text (534):
In step two, the first PVA solution containing the nascent microspheres was rapidly poured into 2.4 liters of cold (4.degree. C.) distilled water. This final bath was mixed gently at 4.degree. C. for 1 hr with the surface of the solution under nitrogen. After 1 hr, the microspheres were filtered using 0.22 .mu.m filter and washed with 3 liters of distilled water containing 0.1% Tween 20 to reduce agglomeration.

Detailed Description Text (537):
Encapsulated microspheres of Pseudomonas cepacia lipase are prepared by phase separation techniques. The crystalline LPS prepared in Example 43 is encapsulated in polylactic-co-glycolic acid ("PLGA") using a double emulsion method. A 700 mg aliquot of protein crystals is injected in methylene chloride containing PLGA (0.6 g PLGA/ml solvent; 10 ml). The mixture is homogenized for 30 sec at 3,000 rpm, using a homogenizer with a microfine tip. The resulting suspension is transferred to a stirred tank (900 ml) containing 6% poly (vinyl alcohol) ("PVA") and methylene chloride (4.5 ml). The solution is mixed at 1,000 rpm for 1 min. The microspheres in the PVA solution are precipitated by immersion in distilled water, washed and

filtered. The microspheres are then washed with distilled water containing 0.1% Tween, to reduce agglomeration and dried with nitrogen for 2 days at 4.degree. C.

Detailed Description Text (539):
A. Protein Content of Microspheres

Detailed Description Text (540):
The total protein content of the microspheres prepared in Example 48 was measured. Triplicate samples of 25 mg of the PLGA/PVA microspheres were incubated in 1 N sodium hydroxide with mixing for 48 hrs. The protein content was then estimated using Bradford's method (M. M. Bradford, Analytical Biochemistry, vol. 72, page 248-254 (1976)) and a commercially available kit from BioRad Laboratories (Hercules, Calif.). The protein containing microspheres were compared to PLGA microspheres without any crystals and is shown in Table 14.

Detailed Description Text (543):
Protein Release from Microspheres

Detailed Description Text (544):
The release of protein from the PLGA microspheres prepared in Example 48 was measured by placing 50 mg of protein encapsulated PLGA microspheres in microcentrifuge filtration tubes containing 0.22 .mu.m filters. Next, 600 .mu.l of release buffer (phosphate buffered saline with 0.02% Tween 20 at pH 7.4) was added to the microspheres on the retentate side of the filter. The tubes were incubated at 37.degree. C. to allow dissolution. To measure the amount of protein released with time, samples were taken at different time intervals. The tube was centrifuged at 3000 rpm for 1 minute and the filtrate was removed for protein activity and total protein measurements. The microspheres were then resuspended with another 600 .mu.l of release buffer.

Detailed Description Text (545):
A. Total Protein Released From Microspheres

Detailed Description Text (548):
These data illustrate that the encapsulated proteins of this invention are suitable for biological delivery of therapeutic proteins. Various rates of delivery can be selected by manipulating the choice of protein crystal, size of the crystals, crosslinking of the crystals, the hydrophobic and hydrophilic characteristics of the encapsulating polymer, the number of encapsulations, dose of microspheres and other easily controllable variables.

Detailed Description Text (549):
B. Protein Activity Released From Microspheres

Detailed Description Text (550):
The biological activity of the protein released with time was measured using the olive oil assay for lipase microspheres. These results are shown in Table 17.

Detailed Description Text (551):
The biological activity of the released protein, as shown in Table 17, demonstrates that the microspheres protect and release active protein. The cumulative percent activity released, calculated based on the amount of input protein, was closely correlated with the total protein released (compare Table 16 and Table 17). The two different crystal lipases released essentially 100% active protein. Even after 7 days of immersion at 37.degree. C., the protein that was released from the microspheres was fully active.

Detailed Description Text (554):
Microscopic Examination of PLGA Microspheres

Detailed Description Text (555):
In order to visualize whether the crystals were intact after encapsulation, PLGA microspheres prepared according to Example 48 were examined under an Olympus BX60 microscope equipped with DXC-970MD 3CCD Color Video Camera with Camera Adapter (CMA D2) with Image ProPlus software. Samples of dry microspheres were covered with a glass coverslip, mounted and examined under 10.times. magnification, using an Olympus microscope with an Olympus UPLAN F1 objective lens 10.times./0.30 PH1 (phase contrast), the crystals were readily visualized and the crystal size determined. Microsphere and crystal sizes were determined using Image Pro Software from Olympus and 0.5-150 .mu.m sizing beads provided by the manufacturer. The size of the outer PLGA microspheres was determined, as well as for the crystals.

Detailed Description Text (556):
FIG. 17 depicts crosslinked enzyme crystals of lipase from Candida rugosa encapsulated by the method of Example 48. The crystal size was approximately 25 .mu.m and the microspheres were approximately 90 .mu.m. The magnification was 250.times..

Detailed Description Text (557):
FIG. 18 depicts uncrosslinked enzyme crystals of lipase from Candida rugosa encapsulated by the method of Example 48. The crystal size was approximately 25 .mu.m and the microspheres were approximately 120 .mu.m. The magnification was 250.times..

Detailed Description Text (558):
FIG. 19 depicts crosslinked enzyme crystals of Penicillin acylase from Escherichia coli encapsulated by the method of Example 48. The crystal size was approximately 25 .mu.m and the microspheres were approximately 70 .mu.m. The magnification was 250.times..

Detailed Description Text (559):
FIG. 20 depicts uncrosslinked enzyme crystals of Penicillin acylase from Escherichia coli encapsulated by the method of Example 48. The crystal size was approximately 50 .mu.m and the microspheres were approximately 90 .mu.m. The magnification was 250.times..

Detailed Description Text (560):
FIG. 21 depicts crosslinked enzyme crystals of glucose oxidase from Aspergillus niger encapsulated by the method of Example 48. The crystal size ranged from 0.5 to 1 .mu.m and the microspheres were approximately 50 .mu.m. The magnification was 500.times..

Detailed Description Text (561):
FIG. 22 depicts uncrosslinked enzyme crystals of glucose oxidase from Aspergillus niger encapsulated by the method of Example 48. The crystal size ranged from 0.5 to 1 .mu.m and the microspheres were approximately 50 .mu.m. The magnification was 500.times..

Detailed Description Text (562):
FIG. 23 depicts uncrosslinked enzyme crystals of lipase from Pseudomonas cepacia, encapsulated as a slurry in the mother liquor by the method of Example 48. The crystal size was approximately 2.5 .mu.m and the microspheres were approximately 60 .mu.m. The magnification was 500.times..

Detailed Description Text (566):
The release of proteins from the PLGA microspheres is measured by placing 50 mg of PLGA microspheres in micro-centrifuge filtration tubes containing 0.22 .mu.m filters. A 600 .mu.l aliquot of release buffer (10 mM HEPES, pH 7.4, 100 mM NaCl, 0.02% Tween, 0.02% azide) is added to suspend the microspheres on the retentate side of the filter. The tubes are sealed with 3 cc vial stoppers and covered by

parafilm. The microspheres are then incubated at 37.degree. C. Samples are taken over time by centrifugation (13,000 rpm, 1 min) of the tubes. The filtrate is removed and the microspheres are resuspended with 600 .mu.l of the release buffer. The quality of the released protein is assayed by SEC-HPLC and enzymatic activity.

Detailed Description Text (574):
The coated crystals were evaluated by Western blotting to confirm the presence of the albumin layer Following washing, coated protein crystals were incubated in 100 mM NaOH overnight to dissolve the microspheres into the constituent proteins. The samples were neutralized, filtered and analyzed by SDS-PAGE immunoblot according to Sambrook et al. "Molecular Cloning: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989).

Detailed Description Text (575):
The results of SDS-PAGE immunoblot of both albumin coated crosslinked and uncrosslinked crystal microspheres of Candida rugosa lipase revealed a single immunoreactive species having the same molecular weight as albumin.

Detailed Description Text (576):
Samples of the albumin coated crosslinked and uncrosslinked crystal microspheres of Candida rugosa lipase were incubated with a fluorescene-labeled anti-BSA antibodies which specifically recognize and bind to bovine serum albumin. Next, excess antibody was removed thorough washing with phosphate buffer. Microscopic examination of these fluorescently labeled albumin coated crystal microspheres under a fluorscent microscope revealed specific fluorescene-labeling of the microspheres. Uncoated lipase crystals were used as control and these showed no specific binding of the antibody.

Detailed Description Paragraph Table (13):
TABLE 13 Microspheres Produced Crosslinked Crosslinked Crystals Crystals Microspheres Diameter .mu.m Diameter .mu.m Candida rugosa lipase 90 90 Glucose oxidase 50 50 Penicillin acylase 90 70 Lipase from Pseudomonas 60 cepacia (slurry)

Detailed Description Paragraph Table (14):
TABLE 14 Protein Content of Microspheres Protein (%) Protein (%) Crosslinked Uncrosslinked Microspheres Crystals Crystals Unloaded PLGA 0 Microspheres Candida rugosa lipase 30 20 Glucose oxidase 35 28 Penicillin acylase 27 25 Lipase from Pseudomonas 39 cepacia (slurry)

Detailed Description Paragraph Table (15):
TABLE 15 Specific Activity Activity/mg Activity/mg Crosslinked Uncrosslinked Microspheres Crystals Crystals Unloaded PLGA 0 0 Microspheres Candida rugosa lipase 413 Penicillin acylase 9.63 Lipase from Pseudomonas 1414 cepacia (slurry)

Detailed Description Paragraph Table (16):
TABLE 16 Protein Release From Microspheres % Input Pseudomonas % Input Candida cepacia Lipase rugosa lipase Time (hr) Released Released 0 0 0 18 28 2 41 56 5 89 75 10 137 82 22 210 84 34 234 85 47 306 86 70 330 87 86

Current US Cross Reference Classification (1):
424/489

CLAIMS:

12. A microsphere comprising the formulation according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9.

First Hit Fwd Refs

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L3: Entry 1 of 7 File: USPT Apr 1, 2003

US-PAT-NO: 6541606
DOCUMENT-IDENTIFIER: US 6541606 B2

TITLE: Stabilized protein crystals formulations containing them and methods of making them

DATE-ISSUED: April 1, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
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Altus Biologics Inc.	Cambridge	MA			02

APPL-NO: 09/ 374132 [PALM]
DATE FILED: August 10, 1999

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application is a continuation of co-pending International Application PCT/US99/09099, filed Apr. 27, 1999, which claims benefit under 35 U.S.C. .sctn. 119(e) of U.S. provisional application No. 60/083,148 filed on Apr. 27, 1998. This application is also a continuation-in-part of U.S. application 09/224,475, filed on Dec. 31, 1998, which now abandoned, which claims benefit under 35 U.S.C. .sctn. 119(e) of U.S. provisional application No. 60/070,274, filed on Dec. 31, 1997.

INT-CL: [07] C07 K 17/00, C12 N 11/00, C12 N 9/00, A61 K 38/43, A61 K 9/50

US-CL-ISSUED: 530/350; 530/402, 530/403, 530/813, 530/815, 424/501, 424/489, 424/94.1, 424/94.2, 424/94.5, 424/94.6, 435/39, 435/174, 435/178, 435/181, 435/183, 435/188, 514/2, 514/4
US-CL-CURRENT: 530/350; 424/489, 424/501, 424/94.1, 424/94.2, 424/94.5, 424/94.6, 435/174, 435/178, 435/181, 435/183, 435/188, 435/39, 530/402, 530/403, 530/813, 530/815

FIELD-OF-SEARCH: 424/501, 424/489, 424/94.1, 424/94.2, 424/94.5, 424/94.6, 530/350, 530/402, 530/403, 530/813, 530/815, 435/39, 435/174, 435/178, 435/181, 435/183, 435/188, 514/2, 514/4

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL | Clear

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4606909	August 1986	Bechgaard et al.	424/21
☐	5120650	June 1992	Visuri	435/176
☐	5270194	December 1993	D'Alterio et al.	435/188
☐	5385959	January 1995	Tsaur et al.	523/201
☐	5500223	March 1996	Behan et al.	424/451
☐	5593697	January 1997	Barr et al.	424/490
☐	5601846	February 1997	Milstein et al.	424/499
☐	5603956	February 1997	Mateescu et al.	424/488
☐	5618710	April 1997	Navia et al.	435/174
☐	5734026	March 1998	Florin-Robertsson et al.	530/399
☐	5811406	September 1998	Szoka, Jr. et al.	514/44
☐	5827531	October 1998	Morrison et al.	424/450
☐	5898028	April 1999	Jensen et al.	514/4
☐	5932212	August 1999	Khalaf	424/94.6
☐	6004549	December 1999	Reichert et al.	424/85.4
☐	6004768	December 1999	Navia et al.	435/18
☐	6140475	October 2000	Margolin et al.	530/402

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
1196864	November 1985	CA	
WO 96/18417	June 1996	WO	
WO 96/41873	December 1996	WO	
WO 98/42749	October 1998	WO	
WO 98/46732	October 1998	WO	

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Margolin, IBTECH, vol. 14, pp. 223-230, Jul. 1996.*
Vilenchik et al., J. Am. Chem. Soc., vol. 120, pp. 4290-4294, 1998.*
McPherson et al., Methods of Biochemical Analysis, vol. 23, pp. 249-345, 1976.*
Lalonde et al., J. Am. Chem. Soc., vol. 117, pp. 6845-6852, 1995.*
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D. Fass et al., "Structure of a murine leukemia virus receptor-binding glycoprotein at 2.0 angstrom resolution." Science, 277, 1662-1666 (1997).
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G.F. Gao et al., "Crystal structure of the complex between human CD8.alpha..alpha. and HLA-A2." Nature, 387, 630-634 (1997).
F.J. Hoedemaeker et al., "A single chain Fv fragment of P-glycoprotein-specific monoclonal antibody C219: design, expression, and crystal structure at 2.4 .ANG. resolution." J. Biol. Chem., 272, 29784-29789.
N. Kamiya et al., "Surfactant-coated lipase suitable for the enzymatic resolution of menthol as a biocatalyst in organic media." Biotechnol. Prog., 11, 270-275 (1995).
A.L. Margolin, "Novel crystalline catalysts." TIBTECH, 14, 223-230 (1996).
B.H. Shilton et al., "Crystallization of a soluble form of the Kex1p serine carboxypeptidase from Saccharomyces cerevisiae." Protein Science, 5, 395-397 (1996).
X. Wang et al., "The crystal structure of bovine bile salt activated lipase: insights into the bile salt activation mechanism." Structure, 5, 1209-1218 (1997).

ART-UNIT: 1653

PRIMARY-EXAMINER: Low; Christopher S. F.

ASSISTANT-EXAMINER: Mohamed; Abdel A.

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ABSTRACT:

This invention relates to methods for the stabilization, storage and delivery of biologically active macromolecules, such as proteins, peptides and nucleic acids. In particular, this invention relates to protein or nucleic acid crystals, formulations and compositions comprising them. Methods are provided for the crystallization of proteins and nucleic acids and for the preparation of stabilized protein or nucleic acid crystals for use in dry or slurry formulations. The present invention is further directed to encapsulating proteins, glycoproteins, enzymes, antibodies, hormones and peptide crystals or crystal formulations into compositions for biological delivery to humans and animals. According to this invention, protein crystals or crystal formulations are encapsulated within a matrix comprising a polymeric carrier to form a composition. The formulations and compositions enhance preservation of the native biologically active tertiary structure of the proteins and create a reservoir which can slowly release active protein where and when it is needed. Methods are provided preparing stabilized formulations using pharmaceutical ingredients or excipients and optionally encapsulating them in a polymeric carrier to produce compositions and using such protein crystal formulations and compositions for biomedical applications, including delivery of therapeutic proteins and vaccines. Additional uses for the protein crystal formulations and compositions of this invention involve protein delivery in human food, agricultural feeds, veterinary compositions, diagnostics, cosmetics and personal care compositions.

22 Claims, 24 Drawing figures

L3: Entry 3 of 7 File: USPT Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916596 A
TITLE: Protein stabilized pharmacologically active agents, methods for the preparation thereof and methods for the use thereof

Brief Summary Text (7):
The size of particles and their mode of delivery determines their biological behavior. Strand et al. (in Microspheres-Biomedical Applications, ed. A. Rembaum, pp 193-227, CRC Press (1988)) have described the fate of particles to be dependent on their size. Particles in the size range of a few nanometers (nm) to 100 nm enter the lymphatic capillaries following interstitial injection, and phagocytosis may occur within the lymph nodes. After intravenous/intraarterial injection, particles less than about 2 microns will be rapidly cleared from the blood stream by the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS). Particles larger than about 7 microns will, after intravenous injection, be trapped in the lung capillaries. After intraarterial injection, particles are trapped in the first capillary bed reached. Inhaled particles are trapped by the alveolar macrophages.

Brief Summary Text (13):
Protein microspheres have been reported in the literature as carriers of pharmacological or diagnostic agents. Microspheres of albumin have been prepared by either heat denaturation or chemical crosslinking. Heat denatured microspheres are produced from an emulsified mixture (e.g., albumin, the agent to be incorporated, and a suitable oil) at temperatures between 100.degree. C. and 150.degree. C. The microspheres are then washed with a suitable solvent and stored. Leucuta et al. (International Journal of Pharmaceutics 41:213-217 (1988)) describe the method of preparation of heat denatured microspheres.

Brief Summary Text (14):
The procedure for preparing chemically crosslinked microspheres involves treating the emulsion with glutaraldehyde to crosslink the protein, followed by washing and storage. Lee et al. (Science 213:233-235 (1981)) and U.S. Pat. No. 4,671,954 teach this method of preparation.

Brief Summary Text (15):
The above techniques for the preparation of protein microspheres as carriers of pharmacologically active agents, although suitable for the delivery of water-soluble agents, are incapable of entrapping water-insoluble ones. This limitation is inherent in the technique of preparation which relies on crosslinking or heat denaturation of the protein component in the aqueous phase of a water-in-oil emulsion. Any aqueous-soluble agent dissolved in the protein-containing aqueous phase may be entrapped within the resultant crosslinked or heat-denatured protein matrix, but a poorly aqueous-soluble or oil-soluble agent cannot be incorporated into a protein matrix formed by these techniques.

Brief Summary Text (16):
One conventional method for manufacturing drug-containing nanoparticles comprises dissolving polylactic acid (or other biocompatible, water insoluble polymers) in a water-immiscible solvent (such as methylene chloride or other chlorinated, aliphatic, or aromatic solvent), dissolving the pharmaceutically active agent in

the polymer solution, adding a surfactant to the oil phase or the aqueous phase, forming an oil-in-water emulsion by suitable means, and evaporating the emulsion slowly under vacuum. If the oil droplets are sufficiently small and stable during evaporation, a suspension of the polymer in water is obtained. Since the drug is initially present in the polymer solution, it is possible to obtain by this method, a composition in which the drug molecules are entrapped within particles composed of a polymeric matrix. The formation of microspheres and nanoparticles by using the solvent evaporation method has been reported by several researchers (see, for example, Tice and Gilley, in Journal of Controlled Release 2:343-352 (1985); Bodmeier and McGinity, in Int. J. Pharmaceutics 43:179 (1988); Cavalier et al., in J. Pharm. Pharmacol. 38:249 (1985); and D'Souza et al., WO 94/10980) while using various drugs.

Drawing Description Text (21):
Key differences between the pharmacologically active agents contained in a polymeric shell according to the invention and protein microspheres of the prior art are in the nature of formation and the final state of the protein after formation of the particle, and its ability to carry poorly aqueous-soluble or substantially aqueous-insoluble agents. In accordance with the present invention, the polymer (e.g., a protein) may be crosslinked as a result of exposure to high shear conditions in a high pressure homogenizer. High shear is used to disperse a dispersing agent containing dissolved or suspended pharmacologically active agent into an aqueous solution of a biocompatible polymer, optionally bearing sulfhydryl or disulfide groups (e.g., albumin) whereby a shell of crosslinked polymer is formed around fine droplets of non-aqueous medium. The high shear conditions produce cavitation in the liquid that causes tremendous local heating and results in the formation of superoxide ions that are capable of crosslinking the polymer, for example, by oxidizing the sulfhydryl residues (and/or disrupting existing disulfide bonds) to form new, crosslinking disulfide bonds.

Drawing Description Text (22):
In contrast to the invention process, the prior art method of glutaraldehyde crosslinking is nonspecific and essentially reactive with any nucleophilic group present in the protein structure (e.g., amines and hydroxyls). Heat denaturation as taught by the prior art significantly and irreversibly alters protein structure. In contrast, disulfide formation contemplated by the present invention does not substantially denature the protein. In addition, particles of substantially water insoluble pharmacologically active agents contained within a shell differ from crosslinked or heat denatured protein microspheres of the prior art because the polymeric shell produced by the invention process is relatively thin compared to the diameter of the coated particle. It has been determined (by transmission electron microscopy) that the "shell thickness" of the polymeric coat is approximately 25 nanometers for a coated particle having a diameter of 1 micron (1000 nanometers). In contrast, microspheres of the prior art do not have protein shells, but rather, have protein dispersed throughout the volume of the microsphere.

Drawing Description Text (83):
A number of biocompatible polymers may be employed in the practice of the present invention for the formation of the polymeric shell which surrounds the substantially water insoluble pharmacologically active agents. Essentially any polymer, natural or synthetic, optionally bearing sulfhydryl groups or disulfide bonds within its structure may be utilized for the preparation of a disulfide crosslinked shell about particles of substantially water insoluble pharmacologically active agents. The sulfhydryl groups or disulfide linkages may be preexisting within the polymer structure or they may be introduced by a suitable chemical modification. For example, natural polymers such as proteins, peptides, polynucleic acids, polysaccharides (e.g., starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), proteoglycans, lipoproteins, and so on, are candidates for such modification.

Current US Original Classification (1):
424/489

Other Reference Publication (1):
Burgess et al., "Potential use of albumin microspheres as a drug delivery system. I. Preparation and in vitro release of steroids," International Journal of Pharmaceutics, 39:129-136 (1987).

Other Reference Publication (2):
Chen et al., "Comparison of albumin and casein microspheres as a carrier for doxorubicin," J. Pharm. Pharmacol., 39:978-985 (1987).

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Gupta et al., "Albumin microspheres. III. Synthesis and characterization of microspheres containing adriamycin and magnetite," International Journal of Pharmaceutics, 43:167-177 (1988).

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Other Reference Publication (12):
Willmott & Harrison, "Characterisation of freeze-dried albumin microspheres containing the anti-cancer drug adriamycin," International Journal of Pharmaceutics, 43:161-166 (1988).

Other Reference Publication (17):
Cavalier et al., "The formation and characterization of hydrocortisone-loaded poly ((+.sub.--)-lactide) microspheres" J. Pharm. Pharmacol., 38:249-253 (1985).

Other Reference Publication (20):
Leucuta et al., "Albumin microspheres as a drug delivery system for epirubicin: pharmaceutical, pharmacokinetic and biological aspects" International Journal of Pharmaceutics, 41:213-217 (1988).

L3: Entry 4 of 7 File: USPT Sep 9, 1997

DOCUMENT-IDENTIFIER: US 5665383 A
TITLE: Methods for the preparation of immunostimulating agents for in vivo delivery

Brief Summary Text (5):
The size of particles and their mode of delivery determines their biological behavior. Strand et al. [in Microspheres-Biomedical Applications, ed. A. Rembaum, pp 193-227, CRC Press (1988)] have described the fate of particles to be dependent on their size. Particles in the size range of a few nanometers (nm) to 100 nm enter the lymphatic capillaries following interstitial injection, and phagocytosis may occur within the lymph nodes. After intravenous/intraarterial injection, particles less than about 2 microns will be rapidly cleared from the blood stream by the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS). Particles larger than about 7 microns will, after intravenous injection, be trapped in the lung capillaries. After intraarterial injection, particles are trapped in the first capillary bed reached. Inhaled particles are trapped by the alveolar macrophages.

Brief Summary Text (7):
Protein microspheres have been reported in the literature as carriers of pharmacological or diagnostic agents. Microspheres of albumin have been prepared by either heat denaturation or chemical crosslinking. Heat denatured microspheres are produced from an emulsified mixture (e.g., albumin, the agent to be incorporated, and a suitable oil) at temperatures between 100.degree. C. and 150.degree. C. The microspheres are then washed with a suitable solvent and stored. Leucuta et al. [International Journal of Pharmaceutics Vol. 41:213-217 (1988)] describe the method of preparation of heat denatured microspheres.

Brief Summary Text (8):
The procedure for preparing chemically crosslinked microspheres involves treating the emulsion with glutaraldehyde to crosslink the protein, followed by washing and storage. Lee et al. [Science Vol. 213:233-235 (1981)] and U.S. Pat. No. 4,671,954 teach this method of preparation.

Brief Summary Text (9):
The above techniques for the preparation of protein microspheres as carriers of pharmacologically active agents, although suitable for the delivery of water-soluble agents, are incapable of entrapping water-insoluble ones. This limitation is inherent in the technique of preparation which relies on crosslinking or heat denaturation of the protein component in the aqueous phase of a water-in-oil emulsion. Any aqueous-soluble agent dissolved in the protein-containing aqueous phase may be entrapped within the resultant crosslinked or heat-denatured protein matrix, but a poorly aqueous-soluble or oil-soluble agent cannot be incorporated into a protein matrix formed by these techniques.

Drawing Description Text (2):
FIG. 1 shows a schematic of a polymeric shell prepared in accordance with the present invention. In the Figure, A refers to the insoluble disulfide crosslinked polymeric shell, B refers to the interior of the polymeric shell, which can contain oxygen or other gas, a fluorocarbon containing dissolved oxygen, a biocompatible oil having biologic dissolved therein, a water-in-oil emulsion containing biologic

dissolved in aqueous media, a suspension of solid particles dispersed in a liquid, and the like, C designates the thickness of the polymeric shell, typically about 5-50 nanometers, and D refers to the diameter of the polymeric shell, typically in the range of about 0.1 up to 20 .mu.m.

Detailed Description Text (15):
A number of biocompatible materials may be employed in the practice of the present invention for the formation of a polymeric shell. As used herein, the term "biocompatible" describes a substance that does not appreciably alter or affect in any adverse way, the biological system into which it is introduced. Essentially any material, natural or synthetic, bearing sulfhydryl groups or disulfide bonds within its structure may be utilized for the preparation of a disulfide crosslinked shell. The sulfhydryl groups or disulfide linkages may be preexisting within the structure of the biocompatible material, or they may be introduced by a suitable chemical modification. For example, naturally occurring biocompatible materials such as proteins, polypeptides, oligopeptides, polynucleotides, polysaccharides (e.g., starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), lipids, and so on, are candidates for such modification. Other linkages, such as esters, amides, ethers, and the like, can also be formed during the ultrasonic irradiation step (so long as the requisite functional groups are present on the starting material).

Detailed Description Text (45):
In addition, protein cochleates, which are stable precipitates of protein, phospholipid, and calcium, are new formulations used to enhance the immunogenicity of antigens. The name derives from their unique structure, a rolled-up lipid bilayer maintained by calcium bridges. Membrane proteins or peptides with lipid anchors can be integrated into this lipid bilayer, which protects them from intestinal acid and allows them to be slowly taken up by the Peyer's patches. Protein cochleates can thus be used for presentation of multiple antigens. In experiments with mice, they have been found to stimulate circulating and mucosal antibodies and CTLs (cytotoxic T lymphocytes) that protect against subsequent challenge with pathogen. This approach is currently being tested in animals with influenza, parainfluenza, and HIV vaccines. Such protein cochleates may be encapsulated into polymeric shell microspheres or attached to the walls of the shell to enhance antigenicity of the formulation (Gould-Fogerite, S., J. Exp. Medic. 176:1739 (1992)).

Detailed Description Text (53):
Key differences between the biologic-containing polymeric shell of the invention and protein microspheres of the prior art are in the nature of formation and the final state of the protein after formation of the polymeric shell, and its ability to carry poorly aqueous-soluble or substantially aqueous-insoluble agents. In accordance with the present invention, the polymer (e.g., a protein) is selectively chemically crosslinked through the formation of disulfide bonds through, for example, the amino acid cysteine that occurs in the natural structure of a number of proteins. An ultrasonic irradiation process is used to disperse a dispersing agent containing dissolved or suspended biologic into an aqueous solution of a biocompatible material bearing sulfhydryl or disulfide groups (e.g., albumin) whereby a shell of crosslinked polymer is formed around fine droplets of non-aqueous medium. The ultrasonic irradiation process produces cavitation in the liquid that causes tremendous local heating and results in the formation of superoxide ions that crosslink the polymer by oxidizing the sulfhydryl residues (and/or disrupting existing disulfide bonds) to form new, crosslinking disulfide bonds.

Detailed Description Text (54):
In contrast to the invention process, the prior art method of glutaraldehyde crosslinking is nonspecific and essentially reactive with any nucleophilic group present in the protein structure (e.g., amines, sulfhydryls and hydroxyls). Heat

denaturation as taught by the prior art significantly and irreversibly alters protein structure. In contrast, disulfide formation contemplated by the present invention is very specific, and does not substantially denature the protein. In addition, particles or droplets of biologic contained within a polymeric shell differ from crosslinked or heat denatured protein microspheres of the prior art because the polymeric shell produced by the invention process is relatively thin compared to the diameter of the coated particle. It has been determined (by transmission electron microscopy) that the "shell thickness" of the polymeric coat is approximately 25 nanometers for a coated particle having a diameter of 1 micron (1000 nanometers). In contrast, microspheres of the prior art do not have protein shells, but rather, have protein dispersed throughout the volume of the microsphere.

Detailed Description Text (84):
Examination of insoluble hemoglobin constructs (IHC) of the present invention (microbubbles or microspheres) by circular dichroism revealed that the content of alpha-helices and beta-pleated sheets in the IHC was not significantly different from that of purified stroma free hemoglobin (SFH). This observation is significant because it indicates that the crosslinking procedure and formation of insoluble hemoglobin does not result in denaturation (i.e., the alteration of the tertiary and quaternary structure) of the protein. This observation, of course, is corroborated by functional data showing the retention of reversible oxygen binding and cooperativity between oxygen binding heme units after the synthetic step.

Detailed Description Text (113):
Several drugs are candidates for encapsulation in hemoglobin microspheres of the present invention. Several chemotherapeutic agents require the presence of oxygen for maximal tumor cytotoxicity. The delivery of such drugs within constructs of an oxygen carrier such as hemoglobin effectively combines the essential components of cytotoxicity into a single package. Several useful cytotoxic drugs are oil-soluble. These drugs may be dissolved in a fluorocarbon or other biocompatible oil such as soybean oil, safflower oil, coconut oil, olive oil, cotton seed oil, and the like. The oil/drug solution is subjected to ultrasonic irradiation with a hemoglobin solution to produce microspheres of oil/drug within a shell of crosslinked insoluble hemoglobin. The suspension may be oxygenated prior to intravascular administration. Oil-soluble cytotoxic drugs include cyclophosphamide, BCNU, melphalan, mitomycins, taxol and derivatives, taxotere and derivatives, camptothecin, adriamycin, etoposide, tamoxifen, vinblastine, vincristine and the like; nonsteroidal antiinflammatories such as ibuprofen, aspirin, piroxicam, cimetidine, and the like; steroids such as estrogen, prednisolone, cortisone, hydrocortisone, diflorasone, and the like, drugs such as phenesterine, mitotane, visadine, halonitrosoureas, anthrocyclines, ellipticine, diazepam, and the like; immunosuppressive agents such as cyclosporine, azathioprine, FK506, and the like.

Detailed Description Text (192):
As a control, the above components, absent the protein, did not form a stable miocroemulsion when subjected to ultrasonic irradiation. This result suggests that the protein is essential for formation of microspheres. This is confirmed by scanning electron micrograph and transmission electron micrograph studies as described below.

Detailed Description Text (231):
Solid core polymeric shells containing taxol were prepared as described above (see, for example, Example 3) and suspended in normal saline. The concentration of taxol in the suspension was measured by HPLC as follows. First, the taxol within the polymeric shell was liberated by the addition of 0.1M mercaptoethanol (resulting in exchange of protein disulfide crosslinkages, and breakdown of the crosslinking of the polymeric shell), then the liberated taxol was extracted from the suspension with acetonitrile. The resulting mixture was centrifuged and the supernatant freeze-dried. The lyophilate was dissolved in methanol and injected onto an HPLC to

determine the concentration of taxol in the suspension. The taxol concentration was found to be about 1.6 mg/ml.

Detailed Description Text (269):
A 20 ml glass reaction cell, titanium horn and collar were washed with alcohol and sterile saline prior to synthesis as was all equipment used. In a typical reaction, 3.5 ml of a 5% w/v hemoglobin (human or bovine) was added to a reaction cell which was attached to the ultrasonic horn (Heat Systems XL2020, 20 KHz, 400 W maximum power). A fluorocarbon, perfluorodecalin 3.5 ml, was added to the reaction vessel. The horn and cell were then submerged in a temperature control bath set to 20.degree. C. The pH of the aqueous phase was 6.8. The ultrasonic source turned on at a power setting of 7. Using the manufacturer's nomograph suggested a power output of approximately 150 W/cm.sup.2. The reaction is complete in about 30 seconds. The homogeneous suspension produced contains the microcapsules or microspheres of crosslinked insoluble hemoglobin shells with encapsulated perfluorodecalin in the interior. The milky suspension is filtered, washed, resuspended in sterile buffered saline as above and stored in a sterile container at 4.degree. C.

Detailed Description Text (273):
A 20 ml glass reaction cell, titanium horn and collar were washed with alcohol and sterile saline prior to synthesis as was all equipment used. In a typical reaction, 3.5 ml of a 5% w/v albumin (human or bovine) was added to a reaction cell which was attached to the ultrasonic horn (Heat Systems XL2020, 20 KHz, 400 W maximum power). A fluorocarbon, perfluorodecalin (or perfluorotripropyl amine) 3.5 ml, was added to the reaction vessel. The horn and cell were then submerged in a temperature control bath set to 20.degree. C. The pH of the aqueous phase was 6.8. The ultrasonic source turned on at a power setting of 7. Using the manufacturer's nomograph suggested a power output of approximately 150 W/cm.sup.2. The reaction is complete in about 30 seconds. The homogeneous suspension produced contains the microcapsules or microspheres of crosslinked insoluble Albumin shells with encapsulated perfluorodecalin (or perfluorotripropyl amine) in the interior. The milky suspension is filtered, washed, resuspended in sterile buffered saline as above and stored in a sterile container at 4.degree. C.

Detailed Description Text (295):
The cytotoxic effects of several antineoplastic drugs are greatly enhanced in the presence of oxygen. It is therefore desirable to deliver a drug to a tumor site while increasing oxygen concentration at that site. The hemoglobin microspheres of the present invention allow for that capability. Example 16 above describes the encapsulation of a fluorocarbon liquid in a shell of insoluble hemoglobin. Cytotoxic drugs such as cyclophosphamide, BCNU, Melphalan, taxol, camptothecin, adriamycin, etoposide, and the like, can be dissolved in the fluorocarbon or other suitable oil such as soybean oil and encapsulated into the hemoglobin construct.

Detailed Description Text (302):
Several proteins are candidates for encapsulation into polymeric shells, e.g., hemoglobin, albumin, and the like. For example, as a method of increasing the hemoglobin loading of the IHC, hemoglobin could be encapsulated into the IHC instead of the water soluble drug in Example 23. hemoglobin was dissolved in water at a concentration of 10%. One ml of this aqueous solution was emulsified with 4 ml of soybean oil using Pluronic-65 (block copolymer of polyethylene oxide and polypropylene oxide) to form a stable water-in-oil (W/O) microemulsion. 3.5 ml of a 5% Hemoglobin solution was overlayered with 3.5 ml of this W/O microemulsion containing hemoglobin. The two phase mixture was sonicated for 30 seconds to obtain insoluble hemoglobin constructs containing an encapsulated microemulsion that also contained hemoglobin. This method served to increase the total amount of hemoglobin per microsphere of the IHC and therefore increased the oxygen carrying capacity for bound oxygen.

Current US Cross Reference Classification (3):
424/489

L3: Entry 6 of 7 File: USPT Oct 1, 1996

DOCUMENT-IDENTIFIER: US 5560933 A
TITLE: Methods for in vivo delivery of substantially water insoluble pharmacologically active agents and compositions useful therefor

Brief Summary Text (8):
The size of particles and their mode of delivery determines their biological behavior. Strand et al. [in Microspheres-Biomedical Applications, ed. A. Rembaum, pp 193-227, CRC Press (1988)] have described the fate of particles to be dependent on their size. Particles in the size range of a few nanometers (nm) to 100 nm enter the lymphatic capillaries following interstitial injection, and phagocytosis may occur within the lymph nodes. After intravenous/intraarterial injection, particles less than about 2 microns will be rapidly cleared from the blood stream by the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS). Particles larger than about 7 microns will, after intravenous injection, be trapped in the lung capillaries. After intraarterial injection, particles are trapped in the first capillary bed reached. Inhaled particles are trapped by the alveolar macrophages.

Brief Summary Text (10):
Protein microspheres have been reported in the literature as carriers of pharmacological or diagnostic agents. Microspheres of albumin have been prepared by either heat denaturation or chemical crosslinking. Heat denatured microspheres are produced from an emulsified mixture (e.g., albumin, the agent to be incorporated, and a suitable oil) at temperatures between 100.degree. C. and 150.degree. C. The microspheres are then washed with a suitable solvent and stored. Leucuta et al. [International Journal of Pharmaceutics Vol. 41:213-217 (1988)] describe the method of preparation of heat denatured microspheres.

Brief Summary Text (11):
The procedure for preparing chemically crosslinked microspheres involves treating the emulsion with glutaraldehyde to crosslink the protein, followed by washing and storage. Lee et al. [Science Vol. 213:233-235 (1981)] and U.S. Pat. No. 4,671,954 teach this method of preparation.

Brief Summary Text (12):
The above techniques for the preparation of protein microspheres as carriers of pharmacologically active agents, although suitable for the delivery of water-soluble agents, are incapable of entrapping water-insoluble ones. This limitation is inherent in the technique of preparation which relies on crosslinking or heat denaturation of the protein component in the aqueous phase of a water-in-oil emulsion. Any aqueous-soluble agent dissolved in the protein-containing aqueous phase may be entrapped within the resultant crosslinked or heat-denatured protein matrix, but a poorly aqueous-soluble or oil-soluble agent cannot be incorporated into a protein matrix formed by these techniques.

Drawing Description Text (18):
Key differences between the pharmacologically active agents contained in a polymeric shell according to the invention and protein microspheres of the prior art are in the nature of formation and the final state of the protein after formation of the particle, and its ability to carry poorly aqueous-soluble or

substantially aqueous-insoluble agents. In accordance with the present invention, the polymer (e.g., a protein) is selectively chemically crosslinked through the formation of disulfide bonds through, for example, the amino acid cysteine that occurs in the natural structure of a number of proteins. A sonication process is used to disperse a dispersing agent containing dissolved or suspended pharmacologically active agent into an aqueous solution of a biocompatible polymer bearing sulfhydryl or disulfide groups (e.g., albumin) whereby a shell of crosslinked polymer is formed around fine droplets of non-aqueous medium. The sonication process produces cavitation in the liquid that causes tremendous local heating and results in the formation of superoxide ions that crosslink the polymer by oxidizing the sulfhydryl residues (and/or disrupting existing disulfide bonds) to form new, crosslinking disulfide bonds.

Drawing Description Text (19):
In contrast to the invention process, the prior art method of glutaraldehyde crosslinking is nonspecific and essentially reactive with any nucleophilic group present in the protein structure (e.g., amines and hydroxyls). Heat denaturation as taught by the prior art significantly and irreversibly alters protein structure. In contrast, disulfide formation contemplated by the present invention does not substantially denature the protein. In addition, particles of substantially water insoluble pharmacologically active agents contained within a shell differ from crosslinked or heat denatured protein microspheres of the prior art because the polymeric shell produced by the invention process is relatively thin compared to the diameter of the coated particle. It has been determined (by transmission electron microscopy) that the "shell thickness" of the polymeric coat is approximately 25 nanometers for a coated particle having a diameter of 1 micron (1000 nanometers). In contrast, microspheres of the prior art do not have protein shells, but rather, have protein dispersed throughout the volume of the microsphere.

Drawing Description Text (25):
A number of biocompatible polymers may be employed in the practice of the present invention for the formation of the polymeric shell which surrounds the substantially water insoluble pharmacologically active agents. Essentially any polymer, natural or synthetic, bearing sulfhydryl groups or disulfide bonds within its structure may be utilized for the preparation of a disulfide crosslinked shell about particles of substantially water insoluble pharmacologically active agents. The sulfhydryl groups or disulfide linkages may be preexisting within the polymer structure or they may be introduced by a suitable chemical modification. For example, natural polymers such as proteins, oligopeptides, polynucleic acids, polysaccharides (e.g., starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), and so on, are candidates for such modification.

Detailed Description Text (49):
Solid core polymeric shells containing taxol were prepared as described above (see, for example, Example 4) and suspended in normal saline. The concentration of taxol in the suspension was measured by HPLC as follows. First, the taxol within the polymeric shell was liberated by the addition of 0.1M mercaptoethanol (resulting in exchange of protein disulfide crosslinkages, and breakdown of the crosslinking of the polymeric shell), then the liberated taxol was extracted from the suspension with acetonitrile. The resulting mixture was centrifuged and the supernatant freeze-dried. The lyophilate was dissolved in methanol and injected onto an HPLC to determine the concentration of taxol in the suspension. The taxol concentration was found to be about 1.6 mg/ml.

Current US Original Classification (1):
424/489

L2: Entry 34 of 86 File: USPT Mar 19, 2002

DOCUMENT-IDENTIFIER: US 6359118 B2
TITLE: Carbohydrate crosslinked glycoprotein crystals

Brief Summary Text (64):
Disulfide crosslinkers are described in the Pierce Catalog and Handbook (1997). Examples of such crosslinkers include the symmetric homo-bifunctional, as for example DSS -dithiobis (succinimidyl-propionate), also know as Lomant's Reagent and DTSSP-3-3'-dithiobis (sulfo-succinimidylpropionate), a water soluble version of DSP and many more. Other examples include the heterobifunctional or asymmetric crosslinkers such as SPDP-N-succinimidyl-3-(2-pyridyldithio)propionate and LC-SPDP-succinimidyl-6-(3-[2-pyridyldithio] propionate)hexanoate and others.

Brief Summary Text (73):
Pharmaceutical, personal care, veterinary or prophylactic compositions comprising carbohydrate crosslinked glycoprotein crystals according to this invention may also be selected from the group consisting of tablets, liposomes, granules, spheres, microparticles, microspheres and capsules.

First Hit Fwd Refs

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L2: Entry 56 of 86 File: USPT Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916596 A
TITLE: Protein stabilized pharmacologically active agents, methods for the preparation thereof and methods for the use thereof

Brief Summary Text (7):
The size of particles and their mode of delivery determines their biological behavior. Strand et al. (in Microspheres-Biomedical Applications, ed. A. Rembaum, pp 193-227, CRC Press (1988)) have described the fate of particles to be dependent on their size. Particles in the size range of a few nanometers (nm) to 100 nm enter the lymphatic capillaries following interstitial injection, and phagocytosis may occur within the lymph nodes. After intravenous/intraarterial injection, particles less than about 2 microns will be rapidly cleared from the blood stream by the reticuloendothelial system (RES), also known as the mononuclear phagocyte system (MPS). Particles larger than about 7 microns will, after intravenous injection, be trapped in the lung capillaries. After intraarterial injection, particles are trapped in the first capillary bed reached. Inhaled particles are trapped by the alveolar macrophages.

Brief Summary Text (13):
Protein microspheres have been reported in the literature as carriers of pharmacological or diagnostic agents. Microspheres of albumin have been prepared by either heat denaturation or chemical crosslinking. Heat denatured microspheres are produced from an emulsified mixture (e.g., albumin, the agent to be incorporated, and a suitable oil) at temperatures between 100.degree. C. and 150.degree. C. The microspheres are then washed with a suitable solvent and stored. Leucuta et al. (International Journal of Pharmaceutics 41:213-217 (1988)) describe the method of preparation of heat denatured microspheres.

Brief Summary Text (14):
The procedure for preparing chemically crosslinked microspheres involves treating the emulsion with glutaraldehyde to crosslink the protein, followed by washing and storage. Lee et al. (Science 213:233-235 (1981)) and U.S. Pat. No. 4,671,954 teach this method of preparation.

Brief Summary Text (15):
The above techniques for the preparation of protein microspheres as carriers of pharmacologically active agents, although suitable for the delivery of water-soluble agents, are incapable of entrapping water-insoluble ones. This limitation is inherent in the technique of preparation which relies on crosslinking or heat denaturation of the protein component in the aqueous phase of a water-in-oil emulsion. Any aqueous-soluble agent dissolved in the protein-containing aqueous phase may be entrapped within the resultant crosslinked or heat-denatured protein matrix, but a poorly aqueous-soluble or oil-soluble agent cannot be incorporated into a protein matrix formed by these techniques.

Brief Summary Text (16):
One conventional method for manufacturing drug-containing nanoparticles comprises dissolving polylactic acid (or other biocompatible, water insoluble polymers) in a water-immiscible solvent (such as methylene chloride or other chlorinated, aliphatic, or aromatic solvent), dissolving the pharmaceutically active agent in

the polymer solution, adding a surfactant to the oil phase or the aqueous phase, forming an oil-in-water emulsion by suitable means, and evaporating the emulsion slowly under vacuum. If the oil droplets are sufficiently small and stable during evaporation, a suspension of the polymer in water is obtained. Since the drug is initially present in the polymer solution, it is possible to obtain by this method, a composition in which the drug molecules are entrapped within particles composed of a polymeric matrix. The formation of microspheres and nanoparticles by using the solvent evaporation method has been reported by several researchers (see, for example, Tice and Gilley, in Journal of Controlled Release 2:343-352 (1985); Bodmeier and McGinity, in Int. J. Pharmaceutics 43:179 (1988); Cavalier et al., in J. Pharm. Pharmacol. 38:249 (1985); and D'Souza et al., WO 94/10980) while using various drugs.

Drawing Description Text (21):
Key differences between the pharmacologically active agents contained in a polymeric shell according to the invention and protein microspheres of the prior art are in the nature of formation and the final state of the protein after formation of the particle, and its ability to carry poorly aqueous-soluble or substantially aqueous-insoluble agents. In accordance with the present invention, the polymer (e.g., a protein) may be crosslinked as a result of exposure to high shear conditions in a high pressure homogenizer. High shear is used to disperse a dispersing agent containing dissolved or suspended pharmacologically active agent into an aqueous solution of a biocompatible polymer, optionally bearing sulfhydryl or disulfide groups (e.g., albumin) whereby a shell of crosslinked polymer is formed around fine droplets of non-aqueous medium. The high shear conditions produce cavitation in the liquid that causes tremendous local heating and results in the formation of superoxide ions that are capable of crosslinking the polymer, for example, by oxidizing the sulfhydryl residues (and/or disrupting existing disulfide bonds) to form new, crosslinking disulfide bonds.

Drawing Description Text (22):
In contrast to the invention process, the prior art method of glutaraldehyde crosslinking is nonspecific and essentially reactive with any nucleophilic group present in the protein structure (e.g., amines and hydroxyls). Heat denaturation as taught by the prior art significantly and irreversibly alters protein structure. In contrast, disulfide formation contemplated by the present invention does not substantially denature the protein. In addition, particles of substantially water insoluble pharmacologically active agents contained within a shell differ from crosslinked or heat denatured protein microspheres of the prior art because the polymeric shell produced by the invention process is relatively thin compared to the diameter of the coated particle. It has been determined (by transmission electron microscopy) that the "shell thickness" of the polymeric coat is approximately 25 nanometers for a coated particle having a diameter of 1 micron (1000 nanometers). In contrast, microspheres of the prior art do not have protein shells, but rather, have protein dispersed throughout the volume of the microsphere.

Drawing Description Text (83):
A number of biocompatible polymers may be employed in the practice of the present invention for the formation of the polymeric shell which surrounds the substantially water insoluble pharmacologically active agents. Essentially any polymer, natural or synthetic, optionally bearing sulfhydryl groups or disulfide bonds within its structure may be utilized for the preparation of a disulfide crosslinked shell about particles of substantially water insoluble pharmacologically active agents. The sulfhydryl groups or disulfide linkages may be preexisting within the polymer structure or they may be introduced by a suitable chemical modification. For example, natural polymers such as proteins, peptides, polynucleic acids, polysaccharides (e.g., starch, cellulose, dextrans, alginates, chitosan, pectin, hyaluronic acid, and the like), proteoglycans, lipoproteins, and so on, are candidates for such modification.

Other Reference Publication (1):
Burgess et al., "Potential use of albumin microspheres as a drug delivery system. I. Preparation and in vitro release of steroids," International Journal of Pharmaceutics, 39:129-136 (1987).

Other Reference Publication (2):
Chen et al., "Comparison of albumin and casein microspheres as a carrier for doxorubicin," J. Pharm. Pharmacol., 39:978-985 (1987).

Other Reference Publication (5):
Gupta et al., "Albumin microspheres. III. Synthesis and characterization of microspheres containing adriamycin and magnetite," International Journal of Pharmaceutics, 43:167-177 (1988).

Other Reference Publication (6):
Ishizaka et al., "Preparation of Egg Albumin Microcapsules and Microspheres," Journal of Pharmaceutical Sciences, 70(4):358-363 (1981).

Other Reference Publication (12):
Willmott & Harrison, "Characterisation of freeze-dried albumin microspheres containing the anti-cancer drug adriamycin," International Journal of Pharmaceutics, 43:161-166 (1988).

Other Reference Publication (17):
Cavalier et al., "The formation and characterization of hydrocortisone-loaded poly ((+.sub.--)-lactide) microspheres" J. Pharm. Pharmacol., 38:249-253 (1985).

Other Reference Publication (20):
Leucuta et al., "Albumin microspheres as a drug delivery system for epirubicin: pharmaceutical, pharmacokinetic and biological aspects" International Journal of Pharmaceutics, 41:213-217 (1988).

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L2: Entry 63 of 86 File: USPT Jun 2, 1998

DOCUMENT-IDENTIFIER: US 5759517 A
** See image for Certificate of Correction **
TITLE: Hemoglobins as drug delivery agents

Brief Summary Text (15):
Biocompatable slow-release polymers may be used to release peptides over a period of time. Injectable poly-(D,L) lactic acid/glycolic acid copolymer microspheres have been used for slow release of a polypeptide over the course of a month. Polyethylene glycol and polysaccharide matrices have also been used for similar reasons (Hilvert, Trends in Biotechnology,9(1): 11-17 (1991) and European Patent application 381,719). Surgically implanted polyanhydride disks or "hemispheres" have been experimentally used for slow release of large proteins over a one hundred day period of time. Other methods of drug delivery such as sublingual, oral adsorption and mucosal surface delivery have been explored using a number of potential agents but the slow-release effect has yet to be fully appreciated.

Brief Summary Text (161):
Non-Disulfide Crosslinks. While disulfide linkages are preferred because in vivo reducing agents act to liberate the peptide from the carrier or exogenous reducing agents can be co-administered to modulate half-life, any labile linkage or reversible association may be used. Peptides and other organic compounds may be attached to hemoglobin by alkylation of the cysteine with haloacetyl-peptides or haloacetyl-compounds obtained by direct synthesis. Bifunctional crosslinkers may also be used to bind a chemical to a hemoglobin chain. Yet another example is ester linkages to be cleaved in acidic or alkaline environments. Certain protease cleavage sites for serum proteases could be used as the linker to permit release of the desired chemical. The surrounding microenvironment may be modified by site specific mutagenesis or chemical modification to achieve the desired release rate.

Other Reference Publication (29):
Ebert et al.; On the Introduction of Disulfide Crosslinks into Fibrous Proteins and Bovine Serum Albumin Adv. Exp. Med. Biol. 86A:235-245 (1977).

Other Reference Publication (209):
Rettenmaier et al, Treatment of a Syngeneic Rat Tumor with Magnetically Responsive Albumin Microspheres Labeled with Doxorubicin or Protein A, Gynecologic Oncology, vol. 27, pp. 34-43, 1987.

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Thursday, January 22, 2004

Hide?	Set Name	Query	Hit Count
	DB=USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
☐	L4	L2 and 424/499.ccls.	1
☐	L3	L2 and 424/489.ccls.	7
☐	L2	L1 and microsphere$	86
☐	L1	disulfide adj2 cross$	733

END OF SEARCH HISTORY

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Thursday, January 22, 2004

Hide?	Set Name	Query	Hit Count
	DB=EPAB; PLUR=YES; OP=OR		
☐	L7	L1 and disulfide	0
☐	L6	L1 and cross$link$	1
☐	L5	L1 and (reducing adj2 agent$)	0
☐	L4	WO-2003053414-A2.did.	0
	DB=USPT,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR		
☐	L3	L1 same (reducing adj2 agent$)	3
☐	L2	L1 and (reducing adj2 agent$)	57
☐	L1	(protein$ adj2 microsphere$)	447

END OF SEARCH HISTORY

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Search Results - Record(s) 31 through 57 of 57 returned.

☐ 31. Document ID: US 6124439 A

Using default format because multiple data bases are involved.

L2: Entry 31 of 57 File: USPT Sep 26, 2000

US-PAT-NO: 6124439
DOCUMENT-IDENTIFIER: US 6124439 A

TITLE: OB polypeptide antibodies and method of making

DATE-ISSUED: September 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; Jeffrey M.	New York	NY		
Zhang; Yiying	New York	NY		
Proenca; Ricardo	Astoria	NY		

US-CL-CURRENT: 530/388.24; 424/130.1, 424/133.1, 424/135.1, 424/141.1, 424/142.1, 424/145.1, 424/158.1, 424/178.1, 435/326, 435/328, 435/331, 435/335, 435/336, 435/70.2, 435/70.21, 435/975, 530/387.3, 530/387.9, 530/388.15, 530/388.73, 530/389.1, 530/389.2, 530/391.1, 530/391.3, 530/391.7, 530/864

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 32. Document ID: US 6099856 A

L2: Entry 32 of 57 File: USPT Aug 8, 2000

US-PAT-NO: 6099856
DOCUMENT-IDENTIFIER: US 6099856 A

TITLE: Active agent transport systems

DATE-ISSUED: August 8, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Larchmont	NY		
Barantsevitch; Evgueni	New Rochelle	NY		
Leone-Bay; Andrea	Ridgefield	CT		

Wang; Nai Fang	Long Island City	NY
Sarubbi; Donald J.	Bronxville	NY
Santiago; Noemi B	Hawthorne	NY

US-CL-CURRENT: 424/450; 424/451, 424/464, 424/489, 424/490

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 33. Document ID: US 6083484 A

L2: Entry 33 of 57 File: USPT Jul 4, 2000

US-PAT-NO: 6083484
DOCUMENT-IDENTIFIER: US 6083484 A

TITLE: Microparticles stabilized by polynuclear chromium complexes and their use as ultrasound contrast agents

DATE-ISSUED: July 4, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lohrmann; Rolf	La Jolla	CA		
Golec; Brent Lee	San Diego	CA		

US-CL-CURRENT: 424/9.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 34. Document ID: US 6071538 A

L2: Entry 34 of 57 File: USPT Jun 6, 2000

US-PAT-NO: 6071538
DOCUMENT-IDENTIFIER: US 6071538 A

TITLE: Oral delivery composition comprising supramolecular complex

DATE-ISSUED: June 6, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Larchmont	NY		
Barantsevitch; Evgueni	New Rochelle	NY		
Leone-Bay; Andrea	Ridgefield	CT		
Wang; Nai Fang	Long Island City	NY		
Sarubbi; Donald J.	Bronxville	NY		
Santiago; Noemi B	Hawthorne	NY		

US-CL-CURRENT: 424/464; 424/408, 424/450, 424/451, 424/489, 424/491

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 35. Document ID: US 6048837 A

L2: Entry 35 of 57 File: USPT Apr 11, 2000

US-PAT-NO: 6048837
DOCUMENT-IDENTIFIER: US 6048837 A

TITLE: OB polypeptides as modulators of body weight

DATE-ISSUED: April 11, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; Jeffrey M.	New York	NY		
Zhang; Yiying	New York	NY		
Proenca; Ricardo	Astoria	NY		

US-CL-CURRENT: 514/2; 424/85.1, 514/12, 514/21, 514/8, 514/844, 514/866, 514/909

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 36. Document ID: US 6022709 A

L2: Entry 36 of 57 File: USPT Feb 8, 2000

US-PAT-NO: 6022709
DOCUMENT-IDENTIFIER: US 6022709 A

TITLE: Nucleic acid encoding an altered telomere repeat binding factor

DATE-ISSUED: February 8, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
de Lange; Titia	New York	NY		
van Steensel; Bas	New York	NY		
Bianchi; Alessandro	New York	NY		

US-CL-CURRENT: 435/69.1; 435/243, 435/252.3, 435/320.1, 435/325, 435/410, 536/23.1, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 37. Document ID: US 6020166 A

L2: Entry 37 of 57 File: USPT Feb 1, 2000

US-PAT-NO: 6020166
DOCUMENT-IDENTIFIER: US 6020166 A

TITLE: Nucleic acid encoding an altered telomere repeat binding factor 2

DATE-ISSUED: February 1, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
De Lange; Titia	New York	NY		
Van Steensel; Bas	Seattle	WA		
Bianchi; Alessandro	Geneve			CH

US-CL-CURRENT: 435/69.1; 435/243, 435/252.3, 435/320.1, 435/325, 435/410, 536/23.1, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 38. Document ID: US 6018033 A

L2: Entry 38 of 57 File: USPT Jan 25, 2000

US-PAT-NO: 6018033
DOCUMENT-IDENTIFIER: US 6018033 A
**** See image for Certificate of Correction ****

TITLE: Hydrophilic, hydrophobic, and thermoreversible saccharide gels and forms, and methods for producing same

DATE-ISSUED: January 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Chen; Jun	Hatfield	PA		
BongJo; Seong	West Lafayette	IN		
Park; Kinam	West Lafayette	IN		

US-CL-CURRENT: 536/4.1; 424/456, 424/461, 424/466, 521/109.1, 526/238.2, 536/103, 536/123.1, 536/123.13, 536/17.2, 536/17.3, 536/17.9, 536/18.2, 536/18.5, 536/55.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 39. Document ID: US 5917019 A

L2: Entry 39 of 57 File: USPT Jun 29, 1999

US-PAT-NO: 5917019
DOCUMENT-IDENTIFIER: US 5917019 A

TITLE: Altered telomere repeat binding factor 2

DATE-ISSUED: June 29, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
de Lange; Titia	New York	NY		
Steensel; Bas Van	New York	NY		
Bianchi; Alessandro	New York	NY		

US-CL-CURRENT: 530/358; 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 40. Document ID: US 5859183 A

L2: Entry 40 of 57 File: USPT Jan 12, 1999

US-PAT-NO: 5859183
DOCUMENT-IDENTIFIER: US 5859183 A
**** See image for Certificate of Correction ****

TITLE: Altered telomere repeat binding factor

DATE-ISSUED: January 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
de Lange; Titia	New York	NY		
Steensel; Bas van	New York	NY		
Bianchi; Alessandro	New York	NY		

US-CL-CURRENT: 530/300; 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 41. Document ID: US 5792451 A

L2: Entry 41 of 57 File: USPT Aug 11, 1998

US-PAT-NO: 5792451
DOCUMENT-IDENTIFIER: US 5792451 A

TITLE: Oral drug delivery compositions and methods

DATE-ISSUED: August 11, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sarubbi; Donald J.	Bronxville	NY		

Leone-Bay; Andrea	Ridgefield	CT
Paton; Duncan R.	Purdys	NY

US-CL-CURRENT: 424/85.4; 424/141.1, 424/184.1, 424/465, 424/474, 424/489, 424/491, 424/499, 424/85.2, 514/12, 514/2, 514/21, 514/773

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 42. Document ID: US 5770388 A

L2: Entry 42 of 57 File: USPT Jun 23, 1998

US-PAT-NO: 5770388
DOCUMENT-IDENTIFIER: US 5770388 A

TITLE: Method of separation employing magnetic particles and second medium

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vorpahl; John	Livermore	CA		

US-CL-CURRENT: 435/7.25; 435/7.2, 435/7.21, 435/7.9, 435/7.92, 435/7.94, 436/501, 436/514, 436/518, 436/526, 436/806, 436/824

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 43. Document ID: US 5766633 A

L2: Entry 43 of 57 File: USPT Jun 16, 1998

US-PAT-NO: 5766633
DOCUMENT-IDENTIFIER: US 5766633 A
**** See image for Certificate of Correction ****

TITLE: Oral drug delivery compositions and methods

DATE-ISSUED: June 16, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Larchmont	NY		
Barantsevitch; Evgueni N.	New Rochelle	NY		
Sarubbi; Donald J.	Bronxville	NY		
Leone-Bay; Andrea	Ridgefield	CT		
Paton; Duncan R.	Purdys	NY		

US-CL-CURRENT: 424/489; 424/451, 424/464

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 44. Document ID: US 5718884 A

L2: Entry 44 of 57 File: USPT Feb 17, 1998

US-PAT-NO: 5718884
DOCUMENT-IDENTIFIER: US 5718884 A

TITLE: Microbubble-based contrast agents with crosslinked and reduced proteinaceous shells

DATE-ISSUED: February 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Klaveness; Jo	Oslo			NO
Rongved; Pal	Nesoddtangen			NO
Johansen; John Henrik	Oslo			NO
Foss; Per Antonius	Oslo			NO
H.o slashed.gset; Anders	Oslo			NO
Hvoslef; Anne Marie	S.o slashed.rumsand			NO

US-CL-CURRENT: 424/9.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

☐ 45. Document ID: US 5714167 A

L2: Entry 45 of 57 File: USPT Feb 3, 1998

US-PAT-NO: 5714167
DOCUMENT-IDENTIFIER: US 5714167 A
** See image for Certificate of Correction **

TITLE: Active agent transport systems

DATE-ISSUED: February 3, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Larchmont	NY		
Barantsevitch; Evgueni	New Rochelle	NY		
Leone-Bay; Andrea	Ridgefield	CT		
Wang; Nai Fang	Long Island City	NY		
Sarubbi; Donald J.	Bronxville	NY		
Santiago; Noemi B.	Hawthorne	NY		

US-CL-CURRENT: 424/490; 424/405, 424/408, 424/450, 424/451, 424/488, 424/489,

424/491

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 46. Document ID: US 5690903 A

L2: Entry 46 of 57 File: USPT Nov 25, 1997

US-PAT-NO: 5690903
DOCUMENT-IDENTIFIER: US 5690903 A

TITLE: Loading and conjugating cavity biostructures

DATE-ISSUED: November 25, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hainfeld; James F.	Shoreham	NY	11786	

US-CL-CURRENT: 424/1.49; 424/1.17, 424/1.53, 424/1.69

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 47. Document ID: US 5683694 A

L2: Entry 47 of 57 File: USPT Nov 4, 1997

US-PAT-NO: 5683694
DOCUMENT-IDENTIFIER: US 5683694 A

TITLE: Method for the treatment of tumors with conjugated antibody A5B7 and a prodrug

DATE-ISSUED: November 4, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bagshawe; Kenneth D.	London			GB
Rogers; Gordon T.	London			GB
Sharma; Surinder K.	London			GB

US-CL-CURRENT: 424/178.1; 424/138.1, 424/181.1, 435/183, 530/387.7, 530/388.8, 530/391.7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 48. Document ID: US 5665582 A

L2: Entry 48 of 57 File: USPT Sep 9, 1997

US-PAT-NO: 5665582
DOCUMENT-IDENTIFIER: US 5665582 A
**** See image for Certificate of Correction ****

TITLE: Isolation of biological materials

DATE-ISSUED: September 9, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kausch; Albert P.	Stonington	CT		
Narayanswami; Sandya	Bar Harbor	ME		

US-CL-CURRENT: 435/181; 435/239, 435/820, 536/126, 536/3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. De

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☐ 49. Document ID: US 5632990 A

L2: Entry 49 of 57 File: USPT May 27, 1997

US-PAT-NO: 5632990
DOCUMENT-IDENTIFIER: US 5632990 A

TITLE: Treatment for tumors comprising conjugated antibody A5B7 and a prodrug

DATE-ISSUED: May 27, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bagshawe; Kenneth D.	London			GB
Rogers; Gordon T.	London			GB
Sharma; Surinder K.	London			GB

US-CL-CURRENT: 424/178.1; 424/180.1, 424/193.1, 424/94.1, 435/174, 530/388.8, 530/391.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. De

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☐ 50. Document ID: US 5443813 A

L2: Entry 50 of 57 File: USPT Aug 22, 1995

US-PAT-NO: 5443813
DOCUMENT-IDENTIFIER: US 5443813 A

TITLE: Loading and conjugating cavity biostructures

DATE-ISSUED: August 22, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hainfeld; James F.	Shoreham	NY		

US-CL-CURRENT: 424/1.17; 530/391.3, 530/391.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 51. Document ID: US 5403573 A

L2: Entry 51 of 57 File: USPT Apr 4, 1995

US-PAT-NO: 5403573
DOCUMENT-IDENTIFIER: US 5403573 A

TITLE: Radiolabeled protein composition and method for radiation synovectomy

DATE-ISSUED: April 4, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Day; Delbert E.	Rolla	MO		
Ehrhardt; Gary J.	Columbia	MO		
Zinn; Kurt R.	Columbia	MO		

US-CL-CURRENT: 424/1.29; 424/1.37, 424/1.49, 424/1.69

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 52. Document ID: US 5279936 A

L2: Entry 52 of 57 File: USPT Jan 18, 1994

US-PAT-NO: 5279936
DOCUMENT-IDENTIFIER: US 5279936 A

TITLE: Method of separation employing magnetic particles and second medium

DATE-ISSUED: January 18, 1994

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vorpahl; John	Livermore	CA		

US-CL-CURRENT: 435/6; 435/5, 435/7.1, 435/7.92, 435/7.93, 435/7.94, 435/7.95, 436/501, 436/512, 436/513, 436/518, 436/526, 436/536, 436/538

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 53. Document ID: US 4783336 A

L2: Entry 53 of 57 File: USPT Nov 8, 1988

US-PAT-NO: 4783336
DOCUMENT-IDENTIFIER: US 4783336 A

TITLE: Polyacrolein-type microspheres

DATE-ISSUED: November 8, 1988

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Margel; Shlomo	Rehovot			IL
Beitler; Uzi	Rehovot			IL

US-CL-CURRENT: 424/462; 424/497, 424/94.3, 427/213.34, 428/402.24, 428/407, 436/501, 436/532, 436/547, 523/223, 524/547 , 526/315, 526/909

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. De

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☐ 54. Document ID: US 4552812 A

L2: Entry 54 of 57 File: USPT Nov 12, 1985

US-PAT-NO: 4552812
DOCUMENT-IDENTIFIER: US 4552812 A
**** See image for Certificate of Correction ****

TITLE: Process for the production of polyacrolein microspheres and grafted microspheres

DATE-ISSUED: November 12, 1985

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Margel; Shlomo	Rehovot			IL
Beitler; Uzi	Rehovot			IL

US-CL-CURRENT: 428/407; 424/178.1, 424/497, 424/94.3, 427/213.34, 428/402.24, 435/180, 435/7.24, 435/7.25, 436/177, 436/501, 436/547, 514/2, 523/223, 524/457, 525/54.1, 526/315, 526/909, 530/391.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. De

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☐ 55. Document ID: US 4197220 A

L2: Entry 55 of 57 File: USPT Apr 8, 1980

US-PAT-NO: 4197220
DOCUMENT-IDENTIFIER: US 4197220 A

TITLE: Impregnated metal-polymeric functional beads

DATE-ISSUED: April 8, 1980

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rembaum; Alan	Altadena	CA		
Volksen; Willi	Pasadena	CA		

US-CL-CURRENT: 525/54.1; 436/56, 436/86, 524/900, 525/337, 525/354, 525/362, 525/363, 525/364

☐ 56. Document ID: JP 63207382 A

L2: Entry 56 of 57 File: JPAB Aug 26, 1988

PUB-NO: JP363207382A
DOCUMENT-IDENTIFIER: JP 63207382 A
TITLE: PRODUCTION OF CARRIER FOR CELL CULTURE

PUBN-DATE: August 26, 1988

INVENTOR-INFORMATION:

NAME	COUNTRY
YASUDA, KENJI	
TAI, SEIJI	
KITAJIMA, MASAAKI	
KANAYAMA, HISANORI	

US-CL-CURRENT: 435/182
INT-CL (IPC): C12N 5/02; C12M 3/02

☐ 57. Document ID: US 20030129252 A1, WO 2003053414 A2

L2: Entry 57 of 57 File: DWPI Jul 10, 2003

DERWENT-ACC-NO: 2003-627277
DERWENT-WEEK: 200360

TITLE: Proteinoid microsphere useful for treatment of wounds comprises a mixture of amino acids that are thermally condensed and cross-linked with a cross linker that can form a pore upon exposure to a reducing agent

INVENTOR: QUIRK, S

PRIORITY-DATA: 2001US-0027441 (December 20, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20030129252 A1	July 10, 2003		000	A61K009/14
WO 2003053414 A2	July 3, 2003	E	022	A61K009/16

INT-CL (IPC): A61 K 9/14; A61 K 9/16; A61 K 9/50

Terms	Documents
L1 and (reducing adj2 agent$)	57

Hit List

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Search Results - Record(s) 1 through 30 of 57 returned.

☐ 1. Document ID: US 6660498 B1

Using default format because multiple data bases are involved.

L2: Entry 1 of 57 File: USPT Dec 9, 2003

US-PAT-NO: 6660498
DOCUMENT-IDENTIFIER: US 6660498 B1

TITLE: Malaria immunogenic composition

DATE-ISSUED: December 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hui; George S. N.	Honolulu	HI		
Pang; Lap-Yin	Kwai Chung			HK
Ho; Walter K. K.	Taipo			HK

US-CL-CURRENT: 435/69.1; 435/69.3, 530/412, 530/413, 530/414, 530/415, 530/416, 530/417

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 2. Document ID: US 6632457 B1

L2: Entry 2 of 57 File: USPT Oct 14, 2003

US-PAT-NO: 6632457
DOCUMENT-IDENTIFIER: US 6632457 B1

TITLE: Composite hydrogel drug delivery systems

DATE-ISSUED: October 14, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sawhney; Amarpreet S.	Bedford	MA		

US-CL-CURRENT: 424/501; 424/486, 424/487

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 3. Document ID: US 6630583 B1

L2: Entry 3 of 57 File: USPT Oct 7, 2003

US-PAT-NO: 6630583
DOCUMENT-IDENTIFIER: US 6630583 B1

TITLE: Antibiotics and methods of using the same

DATE-ISSUED: October 7, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Novak; Rodger	New York	NY		
Tuomanen; Elaine I.	Germantown	TN		

US-CL-CURRENT: 536/23.7; 530/300, 530/324, 530/325, 530/326, 530/327, 530/328, 530/329, 530/350, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | [illegible] | Claims | KWMC | Draw De

☐ 4. Document ID: US 6548056 B2

L2: Entry 4 of 57 File: USPT Apr 15, 2003

US-PAT-NO: 6548056
DOCUMENT-IDENTIFIER: US 6548056 B2

TITLE: Murine interferon-.alpha.

DATE-ISSUED: April 15, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Presnell; Scott R.	Tacoma	WA		
Feldhaus; Andrew L.	Lynnwood	WA		
Gao; Zeren	Redmond	WA		

US-CL-CURRENT: 424/85.7; 424/85.4, 435/69.51, 530/350, 530/351

Full | Title | Citation | Front | Review | Classification | Date | Reference | [illegible] | Claims | KWMC | Draw De

☐ 5. Document ID: US 6544505 B2

L2: Entry 5 of 57 File: USPT Apr 8, 2003

US-PAT-NO: 6544505
DOCUMENT-IDENTIFIER: US 6544505 B2

TITLE: Interferon-epsilon

DATE-ISSUED: April 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Conklin; Darrell C.	Seattle	WA		
Grant; Francis J.	Seattle	WA		
Rixon; Mark W.	Issaquah	WA		
Kindsvogel; Wayne	Seattle	WA		

US-CL-CURRENT: 424/85.4; 424/185.1, 435/69.51, 530/350, 530/351

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 6. Document ID: US 6541606 B2

L2: Entry 6 of 57 File: USPT Apr 1, 2003

US-PAT-NO: 6541606
DOCUMENT-IDENTIFIER: US 6541606 B2

TITLE: Stabilized protein crystals formulations containing them and methods of making them

DATE-ISSUED: April 1, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Margolin; Alexey L.	Newton	MA		
Khalaf; Nazar K.	Worcester	MA		
St. Clair; Nancy L.	Ann Arbor	MI		
Rakestraw; Scott L.	Newark	DE		
Shenoy; Bhami C.	Woburn	MA		

US-CL-CURRENT: 530/350; 424/489, 424/501, 424/94.1, 424/94.2, 424/94.5, 424/94.6, 435/174, 435/178, 435/181, 435/183, 435/188, 435/39, 530/402, 530/403, 530/813, 530/815

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 7. Document ID: US 6524836 B2

L2: Entry 7 of 57 File: USPT Feb 25, 2003

US-PAT-NO: 6524836
DOCUMENT-IDENTIFIER: US 6524836 B2

TITLE: Zace1: a human metalloenzyme

DATE-ISSUED: February 25, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sheppard; Paul O.	Granite Falls	WA	98252	

US-CL-CURRENT: 435/226; 435/252.3, 435/320.1, 435/69.1, 435/69.7, 536/23.2, 536/23.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 8. Document ID: US 6506587 B2

L2: Entry 8 of 57 File: USPT Jan 14, 2003

US-PAT-NO: 6506587
DOCUMENT-IDENTIFIER: US 6506587 B2

TITLE: TRF 1 binding protein, methods of use thereof

DATE-ISSUED: January 14, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
De Lange; Titia	New York	NY		
Smith; Susan	New York	NY		

US-CL-CURRENT: 435/193; 435/320.1, 536/23.1, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

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☐ 9. Document ID: US 6495139 B2

L2: Entry 9 of 57 File: USPT Dec 17, 2002

US-PAT-NO: 6495139
DOCUMENT-IDENTIFIER: US 6495139 B2
**** See image for Certificate of Correction ****

TITLE: Identification and characterization of novel pneumococcal choline binding protein, CBPG, and diagnostic and therapeutic uses thereof

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tuomanen; Elaine I.	Germantown	TN		
Gosink; Khoosheh	Cordova	TN		
Masure; Robert	Germantown	TN		

US-CL-CURRENT: 424/190.1; 424/184.1, 424/185.1, 424/244.1, 530/300, 530/324, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 10. Document ID: US 6485938 B1

L2: Entry 10 of 57 File: USPT Nov 26, 2002

US-PAT-NO: 6485938
DOCUMENT-IDENTIFIER: US 6485938 B1

TITLE: Nucleic acid molecules that encodes human Zven1

DATE-ISSUED: November 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sheppard; Paul O.	Granite Falls	WA		
Bishop; Paul D.	Fall City	WA		

US-CL-CURRENT: 435/69.1; 424/198.1, 435/252.1, 435/254.11, 435/254.2, 435/320.1, 435/325, 435/340, 435/348, 435/410, 530/324, 530/350, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 11. Document ID: US 6471956 B1

L2: Entry 11 of 57 File: USPT Oct 29, 2002

US-PAT-NO: 6471956
DOCUMENT-IDENTIFIER: US 6471956 B1

TITLE: Ob polypeptides, modified forms and compositions thereto

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; Jeffrey M.	New York	NY		
Zhang; Yiying	New York	NY		
Proenca; Ricardo	Astoria	NY		

US-CL-CURRENT: 424/85.1; 514/12, 514/2, 514/8, 530/300, 530/350, 530/351, 530/402

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

☐ 12. Document ID: US 6461643 B2

L2: Entry 12 of 57 File: USPT Oct 8, 2002

US-PAT-NO: 6461643
DOCUMENT-IDENTIFIER: US 6461643 B2

TITLE: Oral drug delivery compositions and methods

DATE-ISSUED: October 8, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Larchmont	NY		
Barantsevitch; Evgueni N.	New Rochelle	NY		
Sarubbi; Donald J.	Bronxville	NY		
Leone-Bay; Andrea	Ridgefield	CT		
Paton; Duncan R.	Purdys	NY		

US-CL-CURRENT: 424/489; 424/451, 424/464, 424/490, 424/491, 424/499, 514/553, 514/561

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 13. Document ID: US 6448224 B1

L2: Entry 13 of 57 File: USPT Sep 10, 2002

US-PAT-NO: 6448224
DOCUMENT-IDENTIFIER: US 6448224 B1

TITLE: Antibiotics and methods of using the same

DATE-ISSUED: September 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Novak; Rodger	Memphis	TN		
Tuomanen; Elaine I.	Germantown	TN		

US-CL-CURRENT: 514/12; 514/13, 514/14, 514/2, 530/300, 530/324, 530/325, 530/326, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 14. Document ID: US 6429290 B1

L2: Entry 14 of 57 File: USPT Aug 6, 2002

US-PAT-NO: 6429290
DOCUMENT-IDENTIFIER: US 6429290 B1

TITLE: OB polypeptides, modified forms and derivatives

DATE-ISSUED: August 6, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; Jeffrey M.	New York	NY		
Zhang; Yiying	New York	NY		
Proenca; Ricardo	Astoria	NY		

US-CL-CURRENT: 530/350; 530/351, 530/399, 530/402

☐ 15. Document ID: US 6395482 B1

L2: Entry 15 of 57 File: USPT May 28, 2002

US-PAT-NO: 6395482
DOCUMENT-IDENTIFIER: US 6395482 B1

TITLE: Method of determining susceptibility to schizophrenia

DATE-ISSUED: May 28, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Karayiorgou; Maria	New York	NY		
Gogos; Joseph A.	New York	NY		

US-CL-CURRENT: 435/6; 435/7.1, 435/91.2, 536/23.5, 536/24.31, 536/24.33

☐ 16. Document ID: US 6391343 B1

L2: Entry 16 of 57 File: USPT May 21, 2002

US-PAT-NO: 6391343
DOCUMENT-IDENTIFIER: US 6391343 B1

TITLE: Fibrinogen-coated particles for therapeutic use

DATE-ISSUED: May 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yen; Richard C. K.	Yorba Linda	CA		

US-CL-CURRENT: 424/491; 424/78.06, 427/2.14, 514/2, 514/834, 514/937, 514/951,

516/77

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 17. Document ID: US 6350730 B1

L2: Entry 17 of 57 File: USPT Feb 26, 2002

US-PAT-NO: 6350730
DOCUMENT-IDENTIFIER: US 6350730 B1
**** See image for Certificate of Correction ****

TITLE: OB polypeptides and modified forms as modulators of body weight

DATE-ISSUED: February 26, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; Jeffrey M.	New York	NY		
Zhang; Yiying	New York	NY		
Proenca; Ricardo	Astoria	NY		

US-CL-CURRENT: 514/12; 514/2, 514/8, 514/909, 530/350, 530/421

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 18. Document ID: US 6348207 B1

L2: Entry 18 of 57 File: USPT Feb 19, 2002

US-PAT-NO: 6348207
DOCUMENT-IDENTIFIER: US 6348207 B1
**** See image for Certificate of Correction ****

TITLE: Orally deliverable supramolecular complex

DATE-ISSUED: February 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Larchmont	NY		
Barantsevitch; Evgueni	New Rochelle	NY		
Leone-Bay; Andrea	Ridgefield	CT		
Wang; Nai Fang	Long Island City	NY		
Sarubbi; Donald J.	Bronxville	NY		
Santiago; Noemi B	Hawthorne	NY		

US-CL-CURRENT: 424/408; 424/409, 424/451, 424/464, 424/470, 424/489, 424/498, 424/499

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 19. Document ID: US 6331407 B1

L2: Entry 19 of 57 File: USPT Dec 18, 2001

US-PAT-NO: 6331407
DOCUMENT-IDENTIFIER: US 6331407 B1

TITLE: Antibiotics and methods of using the same

DATE-ISSUED: December 18, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Novak; Rodger	Memphis	TN		
Tuomanen; Elaine I.	Germantown	TN		

US-CL-CURRENT: 435/7.34; 435/243, 435/252.1, 435/253.4, 435/7.2, 435/7.32, 514/12

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 20. Document ID: US 6329175 B1

L2: Entry 20 of 57 File: USPT Dec 11, 2001

US-PAT-NO: 6329175
DOCUMENT-IDENTIFIER: US 6329175 B1

TITLE: Interferon-.epsilon.

DATE-ISSUED: December 11, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Conklin; Darrell C.	Seattle	WA		
Grant; Francis J.	Seattle	WA		
Rixon; Mark W.	Issaquah	WA		
Kindsvogel; Wayne	Seattle	WA		

US-CL-CURRENT: 435/69.51; 435/252.3, 435/254.1, 435/255.1, 435/320.1, 435/325, 435/348, 435/349, 435/410, 530/351, 536/23.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

☐ 21. Document ID: US 6312924 B1

L2: Entry 21 of 57 File: USPT Nov 6, 2001

US-PAT-NO: 6312924
DOCUMENT-IDENTIFIER: US 6312924 B1

TITLE: Murine interferon-.alpha.

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Presnell; Scott R.	Tacoma	WA		
Feldhaus; Andrew L.	Lynnwood	WA		
Gao; Zeren	Redmond	WA		

US-CL-CURRENT: 435/69.51; 435/252.8, 435/254.11, 435/320.1, 435/325, 435/348, 435/349, 435/419, 435/70.5, 514/2, 530/351 , 536/23.1, 536/23.52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 22. Document ID: US 6309853 B1

L2: Entry 22 of 57 File: USPT Oct 30, 2001

US-PAT-NO: 6309853
DOCUMENT-IDENTIFIER: US 6309853 B1

TITLE: Modulators of body weight, corresponding nucleic acids and proteins, and diagnostic and therapeutic uses thereof

DATE-ISSUED: October 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; Jeffrey M.	New York	NY		
Zhang; Yiying	New York	NY		
Proenca; Ricardo	Astoria	NY		

US-CL-CURRENT: 435/69.1; 435/252.3, 435/252.31, 435/252.33, 435/252.34, 435/252.35, 435/320.1, 435/325, 536/23.1, 536/23.5, 536/23.51, 536/24.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw De

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☐ 23. Document ID: US 6280994 B1

L2: Entry 23 of 57 File: USPT Aug 28, 2001

US-PAT-NO: 6280994
DOCUMENT-IDENTIFIER: US 6280994 B1

TITLE: Zace 1: a human metalloenzyme

DATE-ISSUED: August 28, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sheppard; Paul O.	Granite Falls	WA		

US-CL-CURRENT: 435/226; 435/252.3, 435/252.33, 435/320.1, 435/69.1, 435/69.7, 536/23.2, 536/23.4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 24. Document ID: US 6277613 B1

L2: Entry 24 of 57 File: USPT Aug 21, 2001

US-PAT-NO: 6277613
DOCUMENT-IDENTIFIER: US 6277613 B1

TITLE: TRF1 binding protein, methods of use thereof

DATE-ISSUED: August 21, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
De Lange; Titia	New York	NY		
Smith; Susan	New York	NY		

US-CL-CURRENT: 435/193

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. De

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☐ 25. Document ID: US 6248520 B1

L2: Entry 25 of 57 File: USPT Jun 19, 2001

US-PAT-NO: 6248520
DOCUMENT-IDENTIFIER: US 6248520 B1

TITLE: Nucleic acid molecules encoding nuclear hormone receptor coactivators and uses thereof

DATE-ISSUED: June 19, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roeder; Robert G.	New York	NY		
Fondell; Joseph D.	Baltimore	MD		
Xingyuan; Chao	New York	NY		
Ito; Mitsuhiro	New York	NY		

US-CL-CURRENT: 435/6; 435/91.1, 435/91.2, 435/91.21, 435/91.51, 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 26. Document ID: US 6245359 B1

L2: Entry 26 of 57 File: USPT Jun 12, 2001

US-PAT-NO: 6245359
DOCUMENT-IDENTIFIER: US 6245359 B1
**** See image for Certificate of Correction ****

TITLE: Active agent transport systems

DATE-ISSUED: June 12, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Larchmont	NY		
Barantsevitch; Evgueni	New Rochelle	NY		
Leone-Bay; Andrea	Ridgefield	CT		
Wang; Nai Fang	Long Island City	NY		
Sarubbi; Donald J.	Bronxville	NY		
Santiago; Noemi B	Hawthorne	NY		

US-CL-CURRENT: 424/490; 424/450, 424/451, 424/488, 424/489, 424/491

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw De

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☐ 27. Document ID: US 6221367 B1

L2: Entry 27 of 57 File: USPT Apr 24, 2001

US-PAT-NO: 6221367
DOCUMENT-IDENTIFIER: US 6221367 B1

TITLE: Active agent transport systems

DATE-ISSUED: April 24, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Milstein; Sam J.	Larchmont	NY		
Leone-Bay; Andrea	Ridgefield	CT		
Sarubbi; Donald J.	Carmel	NY		
Leipold; Harry	Elmsford	NY		

US-CL-CURRENT: 424/400; 424/489, 424/490, 424/491

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 28. Document ID: US 6193953 B1

L2: Entry 28 of 57 File: USPT Feb 27, 2001

US-PAT-NO: 6193953
DOCUMENT-IDENTIFIER: US 6193953 B1

TITLE: Stabilized microparticles and their use as ultrasound contrast agents

DATE-ISSUED: February 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lohrmann; Rolf	La Jolla	CA		
Golec; Brent Lee	San Diego	CA		

US-CL-CURRENT: 424/9.52; 424/491, 424/499

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 29. Document ID: US 6159502 A

L2: Entry 29 of 57 File: USPT Dec 12, 2000

US-PAT-NO: 6159502
DOCUMENT-IDENTIFIER: US 6159502 A

TITLE: Oral delivery systems for microparticles

DATE-ISSUED: December 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Russell-Jones; Gregory John	Middle Cove			AU
Westwood; Steven William	Ashfield			AU

US-CL-CURRENT: 424/489; 424/491, 424/499, 514/21, 514/52

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw De

☐ 30. Document ID: US 6124448 A

L2: Entry 30 of 57 File: USPT Sep 26, 2000

US-PAT-NO: 6124448
DOCUMENT-IDENTIFIER: US 6124448 A

TITLE: Nucleic acid primers and probes for the mammalian OB gene

DATE-ISSUED: September 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friedman; Jeffrey M.	New York	NY		
Zhang; Yiying	New York	NY		
Proenca; Ricardo	Astoria	NY		
Maffei; Margherita	New York	NY		

US-CL-CURRENT: 536/24.3; 536/24.31

Terms	Documents
L1 and (reducing adj2 agent$)	57